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Ambient Water Quality Criteria for Selenium

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16. ABSTRACT

Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Selenium. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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Office of Water Regulations and Standards
Criteria and Standards Division
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Office of Research and Development
Environmental Criteria and Assessment Office
Cincinnati, Ohio

Carcinogen Assessment Group
Washington, D.C.

Environmental Research Laboratories
Corvalis, Oregon
Duluth, Minnesota
Gulf Breeze, Florida
Narragansett, Rhode Island

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
Deputy Assistant Administrator
Office of Water Regulations and Standards

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Aquatic Life Toxicology:

Charles E. Stephan, ERL-Duluth
U.S. Environmental Protection Agency

John H. Gentile, ERL-Narragansett
U.S. Environmental Protection Agency

Mammalian Toxicology and Human Health Effects:

Dan Greathouse (author) HERL
U.S. Environmental Protection Agency

Debdas Mukerjee (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Donna Sivulka (doc. mgr.) ECAO-Cin
U.S. Environmental Protection Agency

Patrick Durkin
Syracuse Research Corporation

Steven D. Lutkenhoff, ECAO-Cin
U.S. Environmental Protection Agency

Jerry F. Stara, ECAO-Cin
U.S. Environmental Protection Agency

William B. Buck
University of Illinois

John Carroll
U.S. Environmental Protection Agency

Thomas Clarkson
University of Rochester

Terri Laird, ECAO-Cin
U.S. Environmental Protection Agency

Bill Marcus, ODW
U.S. Environmental Protection Agency

Technical Support Services Staff: D.J. Reisman, M.A. Garlough, B.L. Zwayer, P.A. Daunt, K.S. Edwards, T.A. Scandura, A.T. Pressley, C.A. Cooper, M.M. Denessen.

Clerical Staff: C.A. Haynes, S.J. Faehr, L.A. Wade, D. Jones, B.J. Bordicks, B.J. Quesnell, T. Highland, B. Gardiner, R. Swantack.

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CRITERIA DOCUMENT

SELENIUM

CRITERIA

Aquatic Life

For total recoverable inorganic selenite the criterion to protect freshwater aquatic life as derived using the Guidelines is 35 µg/l as a 24-hour average, and the concentration should not exceed 260 µg/l at any time.

For total recoverable inorganic selenite the criterion to protect saltwater aquatic life as derived using the Guidelines is 54 µg/l as a 24-hour average, and the concentration should not exceed 410 µg/l at any time.

The available data for inorganic selenate indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 760 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of inorganic selenate to sensitive freshwater aquatic life.

No data are available concerning the toxicity of inorganic selenate to saltwater aquatic life.

Human Health

The ambient water quality criterion for selenium is recommended to be identical to the existing water standard which is 10 µg/l. Analysis of the toxic effects data resulted in a calculated level which is protective of human health against the ingestion of contaminated water and contaminated aquatic organisms. The calculated value is comparable to the present standard. For this reason a selective criterion based on exposure solely from consumption of 6.5 grams of aquatic organisms was not derived.

INTRODUCTION

Selenium (atomic weight, 78.96) occurs naturally, usually in the presence of the sulfide ores of the heavy metals. It may also be present in small quantities in pyrite, clausthalite, naumannite and tremannite. Selenium exists in several allotrophic forms: amorphous, with a density of 4.28; crystalline, with a density of 4.46, a melting point of approximately 200°C, and a red coloration; and metallic, with a density of 4.81, a melting point of 217°C, and a gray coloration (Windholz, 1976).

Selenium is used in photocopying, the manufacture of glass, electronic devices, pigments, dyes and insecticides (U.S. Dept. Inter., 1974). It is also used in veterinary medicine (Windholz, 1976) and antidandruff shampoos (Cummins and Kimura, 1971). The major source of selenium in the environment is the weathering of rocks and soils (Rosenfeld and Beath, 1964), but human activities contribute about 3,500 metric tons per year (U.S. EPA, 1975).

Selenium reacts with metals to from ionic selenides with a valence of minus 2 and with most other chemicals to form covalent compounds. It may assume any of several valence states ranging from minus 2 to plus 6. Depending on its oxidation state, selenium may act as either an oxidizing agent or a reducing agent [National Academy of Sciences (NAS), 1976]. Inorganic selenium may be converted to organic forms by biological action (NAS, 1976). Biological systems may also convert non-volatile selenium compounds to volatile ones which might escape to air (Chan, et al. 1976).

Solubilities of selenium compounds range from very high (e.g., greater than 40 percent by weight for sodium selenate) to very low (e.g., 16,000 to 33,000 µg/l for the silver selenates) (Chizhikov and Schastlivyi, 1968). Heavy metal selenides are very insoluble (NAS, 1976).

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Aquatic Life Toxicology*

INTRODUCTION

Selenium exists in four oxidation states (-2, 0, +4, and +6). Heavy metal selenides (-2) are insoluble, and hydrogen selenide is a highly reactive gas that decomposes quickly in the presence of oxygen. The elemental form (0) is insoluble and is not rapidly oxidized or reduced in nature and thus becomes a major sink for selenium. The inorganic selenites (+4) have an affinity for iron and aluminum sesquioxides, forming stable absorption complexes. Under acid and reducing conditions the inorganic selenites are reduced to elemental selenium. Alkaline and oxidizing conditions favor the formation and stability of the selenates (+6) which are not tightly complexed by sesquioxides. Because of these chemical and physical properties, the selenates appear to represent a greater hazard than selenites to the environment [National Academy of Sciences (NAS), 1975]. Inorganic selenium may be converted to organic forms by biological action.

Many of the toxicity tests have been conducted with flow-through techniques and measured concentrations. However, the data base for selenium is limited and does not have adequate information to evaluate the influence of hardness and associated alkalinity and pH on the toxicity of selenium. These water quality characteristics would not be expected to have much influence on the solubility and toxicity of selenium.

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*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the Guidelines.

It has been established that selenium is an essential element in animal nutrition. Poston, et al. (1976) have shown that dietary selenium is an essential nutrient for the early life stages of the Atlantic salmon.

The freshwater data base includes only information on the effects of the inorganic selenites and selenates. Patrick, et al. (1975) found that selenate was generally less favorable than selenite to diatoms, while selenate was more favorable than selenite to the growth of blue-green algae. The scud was tested with both selenite and selenate and the LC_{50} value for selenite was about one-half of the LC_{50} for selenate. There does not appear to be great differences in the toxicity of selenites and selenates. The majority of the data base is from results obtained using inorganic selenite.

The selenite data base for saltwater organisms includes results of acute toxicity tests with six invertebrate and seven fish species. Chronic data are available from an early life stage test with the sheepshead minnow and a life cycle test with the mysid shrimp. There are no residue data for saltwater fish or invertebrate species and no data of any kind with selenate.

All test results are expressed as selenium.

EFFECTS

Acute Toxicity

Acute toxicity data are available for five freshwater invertebrate species and selenite (Table 1). The acute values represent moe than two orders of magnitude difference in sensitivity. These values range from 340 µg/l for the scud to 42,400 µg/l for the midge. Both of these species were tested under flow-through conditions with measured concentrations. The EC_{50} values for Daphnia magna ranged from 430 to 2,500 µg/l. The only flow-through test with measured concentrations resulted in a value of 710 µg/l.

Daphnia pulex was less sensitive than Daphnia magna with the EC_{50} value for Daphnia pulex being higher than any of the five values for Daphnia magna. The scud was tested with both selenite and selenate; the selenite was about twice as toxic as the selenate.

As shown in Table 1, the data base for selenite and freshwater fish species has 23 values for eight species of fishes from six taxonomic families. These 96-hour LC_{50} values range from 620 μg/l for the fathead minnow to 28,500 μg/l for the bluegill. Both of these values were determined with flow-through exposures and measured concentrations. The 11 96-hour LC_{50} values of selenite for the fathead minnow ranged from 620 to 11,300 μg/l.

Cardwell, et al. (1976) exposed six fish species as juveniles to selenite as selenium dioxide using flow-through conditions and measured concentrations. The 96-hour LC_{50} values ranged from 2,100 to 28,500 μg/l, which represents an order of magnitude variation in sensitivity. The 96-hour LC_{50} values for fathead minnow fry and juveniles are 2,100 and 5,200 μg/l, respectively, which indicates a possible slight decrease in sensitivity with age, although the difference could be experimental variability.

Adams (1976) found that the acute toxicity of selenite to the fathead minnow was directly related to water temperature with 96-hour LC_{50} values of 10,500 and 11,300 μg/l at 13°C and 2,200 and 3,400 μg/l at 25°C. Adams (1976) also found that the mean of three test values was 11,800 μg/l for selenate as compared to the mean of two tests of 10,900 μg/l for selenite. This result indicates no difference in toxicity due to oxidation state.

In general, fishes were less sensitive to selenite than were invertebrate species (Tables 1 and 3). The 96-hour LC_{50} values for fish species ranged from a species mean acute value of 1,460 μg/l for the fathead minnow to 28,500 μg/l for bluegills. The range of species mean acute values for invertebrate species is from 340 µg/l for the scud to 42,400 µg/l for the midge. The two most sensitive species were crustaceans, and the most resistant species was an insect.

The Freshwater Final Acute Value for inorganic selenite, derived from the Species Mean Acute Values using the calculation procedures in the Guidelines is 263 µg/l (Table 3).

The 96-hour acute values for selenite and six saltwater invertebrate species range from 600 µg/l for juvenile mysid shrimp to 4,600 µg/l for adult blue crabs (Table 1). Glickstein (1978) reported an acute value of 1,040 µg/l for the dungeness crab which is similar to the result of 1,200 µg/l reported for the brown shrimp. The acute values for the congeneric copepods, *Acartia tonsa* and *Acartia clausi*, were 800 and 1,740 µg/l, respectively (U.S. EPA, 1980).

The 96-hour LC_{50} values for selenite and saltwater fishes range from 599 µg/l for haddock larvae (U.S. EPA, 1980) to 67,100 µg/l for the sheepshead minnow (U.S. EPA, 1978). The only flow-through study with measured selenite concentrations was performed with the sheepshead minnow and resulted in a 96-hour LC_{50} of 7,400 µg/l. The saltwater fishes as a group were less sensitive than the invertebrate species although there were cases of individual overlap.

The Saltwater Final Acute Value for inorganic selenite, derived from the Species Mean Acute Values using the calculation procedures in the Guidelines, is 406 µg/l (Table 3).

Chronic Toxicity

Chronic toxicity tests with inorganic selenite have been conducted with two freshwater invertebrate species and two fish species (Table 2). No chronic data are available for any selenate.

Kimball (Manuscript) studied the effects of selenite on survival and reproduction of Daphnia magna in a 28-day renewal test with measured concentrations. The 28-day LC_{50} value was 240 µg/l (Table 6). Survival and reproduction of Daphnia magna exposed to 70 µg/l was similar to survival and reproduction of control animals. Survival at 120 µg/l was 100 percent, but reproduction, expressed as mean young per animal, was only 73 percent of that of control animals. This reduction was statistically significant ($p = 0.05$).

Reading (1979) studied the chronic effects of selenite on the survival, growth, and reproduction of Daphnia pulex in a 28-day renewal test with measured concentrations. Statistical analyses were made on 41 parameters of growth and reproduction. At the exposure concentration of 600 µg/l the number of live young in broods 1 and 2 (of nine broods) was significantly ($p = 0.05$) reduced, and the percentage of dead young in brood 1 was significantly ($p = 0.05$) increased. The adult length of brook 9 (of 10 broods) and total number of embryos in brood 6 (of nine broods) was significantly greater than that of control animals. At the end of the exposure, survival, total number of embryos per animal, and mean brood size was equal to or greater than that of control animals even though, during the exposure, occasional differences were observed. At the exposure concentration of 800 µg/l there was a significant ($p = 0.05$) reduction in preadult mean length of molts 2 and 3 (of four molts) and in mean number of live young in broods 1 and 2 (of nine broods). There also was a significant ($p = 0.05$) increase in the percentage of dead young in broods 1, 2, and 3 (of nine broods). On the other hand, there was a significant ($p = 0.05$) increase in mean adult length of brood 9 (of 10 broods), total number of embryos and number of live young in brood 6 (of nine broods). The mean total number of embryos and live young per animal was only about 60 percent of control animals.

Goettl and Davies (1977) exposed rainbow trout to selenite for 27 months. They found that survival of fish exposed to 60 µg/l was similar to survival of control fish. Survival of fish exposed to 130 µg/l was about one-half that of the control and about 16 percent of these survivors were deformed as compared to no deformed control fish.

Kimball (Manuscript) conducted an early life stage tests with selenite using fathead minnows. Hatchability was not affected at any test concentration. However, posthatch survival of fry exposed to 153 µg/l was only 68 percent as compared to control survival. This increased mortality was statisticaly significant ($p = 0.05$). The mean terminal length, but not weight, of exposed fish was different ($p = 0.05$) than that of control fish. Survival and growth of fish exposed to 83 µg/l were similar to that of control fish.

The ratios between the concentrations in water that cause acute and chronic effects on fish and invertebrate species are small except for the rainbow trout. The acute-chronic ratio for the rainbow trout is about an order of magnitude greater than the other ratios.

The Final Acute-Chronic Ratio of 7.5 for selenite is the geometric mean of the acute-chronic ratios if the atypical ratio of 142 for the rainbow trout is omitted (Table 3). The Freshwater Final Acute Value of 263 µg/l divided by the Final Acute-Chronic Ratio of 7.5 results in the Freshwater Final Chronic Value for selenite of 35 µg/l (Table 3).

Chronic toxicity studies were conducted on impairment of growth during the early life stages of the sheepshead minnow and on reproductive effects in the life cycle of the mysid shrimp (Table 2). The sheepshead minnow chronic value of 675 µg/l was about five times higher than the chronic value of 135 µg/l for the mysid shrimp (U.S. EPA, 1978). The 96-hour LC_{50} for the sheepshead minnow in the same study was 7,400 µg/l, resulting in an acute-chronic ratio of 11. Similarly, the 96-hour LC_{50} for the mysid shrimp of 600 µg/l (U.S. EPA, 1978) results in an acute-chronic ratio of 4.4. It appears that as species sensitivity increases, the ratio of acute to chronic toxicity decreases. The chronic value for the sheepshead, 675 µg/l, is similar to the 96-hour LC_{50} value (600 µg/l) for the mysid shrimp.

The Final Acute-Chronic Ratio of 7.5 for inorganic selenite is the geometric mean of the acute-chronic ratios if the atypical ratio of 142 for the rainbow trout is omitted (Table 3). The Saltwater Final Acute Value of 406 µg/l divided by the Final Acute-Chronic Ratio of 7.5 results in the Saltwater Final Chronic Value for selenite of 54 µg/l.

Plant Effects

Data for the toxic effects of selenium on five freshwater algal species are listed in Table 4. An unspecified selenium compound was quite toxic to two green algal species (Hutchinson and Stokes, 1975) with growth being retarded at 50 µg/l. These results indicate that further investigation is needed with regard to toxic effects of selenium on plants. Kumar and Prakash (1971) tested two algal species with selenite and selenate and observed no difference in toxicity (Table 4).

One saltwater algal species, Skeletonema costatum, has been exposed to selenite acid resulting in 96-hour EC_{50} values of 8,200 µg/l for population decrease measured by cell counts and 7,930 µg/l using chlorophyll a (U.S. EPA, 1978). These values are similar to the acute toxicity values reported for the saltwater fishes and 2 to 10 times higher than those reported for the saltwater invertebrate species.

In all of the tests with plants, concentrations were not measured, and thus there are no Freshwater or Saltwater Final Plant Values.

Residues

Bioconcentration factors for selenite have been determined for the rainbow trout, fathead minnow, and bluegill (Table 5). These factors ranged from 8 to 78 for whole body and from 15 to 18 for muscle. The tissue half-life for the bluegill exposed for 28 days was between one and seven days (U.S. EPA, 1978). However, Adams (1976) found that selenite appeared to reach steady state in the fathead minnow at 96 days, and that the half-life of selenite in whole fish was 62.9 days. There are no laboratory studies on the role of dietary selenite as related to tissue concentration. Adams (1976) suggested that dietary selenite in natural systems plays an important role in residue levels in fishes.

Miscellaneous

Except for the rainbow trout (Adams, 1976), the data for freshwater aquatic life in Tables 1 and 6 clearly indicate that selenite causes increasing cumulative mortality with increasing time of exposure past 96 hours. Hodson, et al. (1980) reported that the mean LC_{50} value for three tests with 8,100 µg/l for four days of exposure and decreased to 6,500 µg/l after nine days. There also was delayed mortality during a 4-day period following cessation of the selenite exposure.

Cumulative mortality due to selenite has been found in other fish species. Kimball (Manuscript), Cardwell, et al. (1976), and Halter, et al. (1980) exposed fathead minnows for 8, 9, and 14 days, respectively, and they found that LC_{50} values decreased to about one-half those after 96 hours. Halter, et al. (1980) did not find a lethal threshold after 17 days. Adams (1976) reported that the toxicity curve for fathead minnows was not asymptomatic with the time axis after 48 days of exposure. Cardwell, et al. (1976) also found that the goldfish and bluegill were more sensitive to exposure beyond 96 hours.

Freshwater invertebrate species also appear to be susceptible to the cumulative lethal effects of selenite. Halter, et al. (1980) reported a 14-day LC_{50} value for scud of 70 μg/l. They indicated that this toxicity may have been influenced by ingested selenium, since a contaminated food source was available throughout the exposure. This 14-day LC_{50} was about one-fifth of the 96-hour value. They continued the exposure for a total of 21 days and found that survival and apparent health of the scud exposed to 30 μg/l was similar to that of control animals. They also exposed *Daphnia magna* for 14 days. The 48-hour LC_{50} value was about twice that of the 96-hour value. However, the LC_{50} value did not change between 96 hours and 14 days.

Only one of the freshwater effect values in Table 6 is for selenate. Adams (1976) found that in a 48-day exposure of the fathead minnow selenite was slightly more lethal than selenate.

Hodson, et al. (1980) reported on the chronic effects of sodium selenite on rainbow trout. After exposure for 23 weeks posthatch there was no statistically significant ($p = 0.05$) adverse effect on any measured physiological parameter. After exposure for 50 weeks posthatch they found a significant ($p = 0.05$) effect on blood iron at selenite concentrations of 16 and 53 μg/l, but no effect at the intermediate concentration of 27 μg/l. They suggested that rainbow trout respond to selenite at concentrations less than or equal to 53 μg/l, but that the low level of these responses suggested little harm during long exposure. Hodson, et al. (1980) also reported on the effects of selenite on embryo development, hatching, and fry survival. For the controls 18.4 percent of the embryos did not reach the eyed stage, and there was a 3 percent mortality of eyed embryos and 6.4 percent mortality of sac and swim-up fry; the corresponding percentages for fish exposed to 47 µg/l were 18.6, 6.5, and 5.0, respectively. The mean wet weight of these fry was 0.28 gram which was greater than the mean wet weight of 0.25 gram for the control fish. The 6.5 percent mortality of eyed embryos exposed to 47 µg/l was about twice that of control mortality and was significant ($p = 0.05$). Because the total mortality of embryos and fry exposed to 47 µg/l was only slightly more than the mortality of controls and the mean weight of exposed fry was greater than that of control fry, this statistical effect is not thought to be ecologically significant. The high concentration of 47 µg/l is marginally safe. Thus these data are included in Table 6.

Saltwater studies were conducted by Glickstein (1978) on the effects of selenite on embryos of the Pacific oyster. Sodium selenite and selenium oxide were tested but no toxicity was reported for either compound at concentrations up to 10,000 µg/l. This would indicate that the molluscan larvae are much less sensitive than other invertebrate species tested.

Summary

Acute toxicity data for inorganic selenite are available for 13 species of freshwater animals from 10 different taxonomic families and range from 340 to 42,400 µg/l. Data for 10 species are available from flow-through tests with measured concentrations. Most of the data has been derived for selenite which may be slightly more toxic than selenate. Selenite is a cumulative toxicant to both fish and invertebrate species with mortality commonly occurring well beyojnd the usual four days for standard testing. Chronic data for selenite are available for two cladoceran and two fish species. Except for the rainbow trout, the acute-chronic ratios range from 5.6 to 13. The plant data indicate that green algae may be more sensitive than animals. The lowest effect level for plants is 50 µg/l. Fish muscle and whole fish bioconcentration factors range from 8 to 78.

The saltwater acute values for inorganic selenite and fishes ranged from 599 µg/l for haddock to 67,100 µg/l for the sheepshead minnow. The acute values for the invertebrate species ranged from 600 to 4,600 µg/l, indicating that they were generally more sensitive than the fishes. Chronic studies conducted with the sheepshead minnow and mysid shrimp resulted in chronic values of 675 and 135 µg/l, respectively, for selenite. The acute-chronic ratio was greater (11) for the less sensitive sheepshead than the mysid (4.4). Plant studies with an alga resulted in decreased cell numbers at 8,200 µg/l. Acute toxicity to Pacific oyster embryos occurred at concentrations greater than 10,000 µg/l indicating that this group is not sensitive to acute selenite toxicity. Tissue residue data were not available for selenite, nor were there data showing the influence of environmental factors on selenite toxicity.

CRITERIA

For toal recoverable inorganic selenite the criterion to protect freshwater aquatic life as derived using the Guidelines is 35 µg/l as a 24-hour average and the concentration should not exceed 260 µg/l at any time.

For total recoverable inorganic selenite the criterion to protect saltwater aquatic life as derived using the Guidelines is 54 µg/l as a 24-hour average and the concentration should not exceed 410 µg/l at any time.

The available data for inorganic selenate indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 760 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of inorganic selenate to sensitive freshwater aquatic life.

No data are available concerning the toxicity of inorganic selenate to saltwater aquatic life.

Table 1. Acute values for selenium

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
		FRESHWATER SPECIES			
		Selenite			
Snail, *Physa* sp.	S, U	Sodium selenite	24,100	24,100	Reading, 1979
Cladoceran, *Daphnia magna*	S, U	Sodium selenite	2,500	-	Bringmann & Kuhn, 1959
Cladoceran, *Daphnia magna*	FT, M	Sodium selenite	710	-	Halter, et al. 1980
Cladoceran, *Daphnia magna*	S, M	Selenous acid	1,220	-	Kimball, Manuscript
Cladoceran, *Daphnia magna*	S, M	Selenous acid	1,220	-	Kimball, Manuscript
Cladoceran, *Daphnia magna*	S, U	Selenous acid	430	710	U.S. EPA, 1978
Cladoceran, *Daphnia pulex*	S, M	Sodium selenite	3,870	3,870	Reading, 1979
Scud, *Hyallela azteca*	FT, M	Sodium selenite	340	340	Halter, et al. 1980
Midge, *Tanytarsus dissimilis*	FT, M	Selenium dioxide	42,400	42,400	U.S. EPA, 1980
Rainbow trout, *Salmo gairdneri*	S, U	Sodium selenite	4,500	-	Adams, 1976
Rainbow trout, *Salmo gairdneri*	S, U	Sodium selenite	4,200	-	Adams, 1976
Rainbow trout, *Salmo gairdneri*	FT, M	Sodium selenite	12,500	-	Goettl & Davies, 1976
Rainbow trout, *Salmo gairdneri*	FT, M	Sodium selenite	7,200	-	Hodson, et al. 1980

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
Rainbow trout, Salmo gairdneri	FT, M	Sodium selenite	8,200	-	Hodson, et al. 1980
Rainbow trout, Salmo gairdneri	FT, M	Sodium selenite	8,800	9,000	Hodson, et al. 1980
Brook trout (adult), Salvelinus fontinalis	FT, M	Selenium dioxide	10,200	10,200	Cardwell, et al. 1976
Goldfish, Carassius auratus	FT, M	Selenium dioxide	26,100	26,100	Cardwell, et al. 1976
Fathead minnow, Pimephales promelas	S, U	Sodium selenite	10,500	-	Adams, 1976
Fathead minnow, Pimephales promelas	S, U	Sodium selenite	11,300	-	Adams, 1976
Fathead minnow, Pimephales promelas	S, U	Sodium selenite	6,000	-	Adams, 1976
Fathead minnow, Pimephales promelas	S, U	Sodium selenite	7,400	-	Adams, 1976
Fathead minnow, Pimephales promelas	S, U	Sodium selenite	3,400	-	Adams, 1976
Fathead minnow, Pimephales promelas	S, U	Sodium selenite	2,200	-	Adams, 1976
Fathead minnow (fry), Pimephales promelas	FT, M	Selenium dioxide	2,100	-	Cardwell, et al. 1976
Fathead minnow (juvenile), Pimephales promelas	FT, M	Selenium dioxide	5,200	-	Cardwell, et al. 1976
Fathead minnow, Pimephales promelas	FT, M	Sodium selenite	1,000	-	Halter, et al. 1980
Fathead minnow, Pimephales promelas	FT, M	Selenous acid	620	-	Kimball, Manuscript

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
Fathead minnow, *Pimephales promelas*	FT, M	Selenous acid	970	1,460	Kimball, Manuscript
Channel catfish, *Ictalurus punctatus*	FT, M	Selenium dioxide	13,600	13,600	Cardwell, et al. 1976
Flagfish, *Jordanella floridae*	FT, M	Selenium dioxide	6,500	6,500	Cardwell, et al. 1976
Mosquitofish, *Gambusia affinis*	S, U	Sodium selenite	12,600	12,600	Reading, 1979
Bluegill, *Lepomis macrochirus*	FT, M	Selenium dioxide	28,500	28,500	Cardwell, et al. 1976
		Selenate			
Scud, *Hyallela azteca*	FT, M	Sodium selenate	760	760	Adams, 1976
Fathead minnow, *Pimephales promelas*	S, U	Sodium selenate	11,800	-	Adams, 1976
Fathead minnow, *Pimephales promelas*	S, U	Sodium selenate	11,000	-	Adams, 1976
Fathead minnow, *Pimephales promelas*	S, U	Sodium selenate	12,500	12,000	Adams, 1976
		SALTWATER SPECIES			
		Selenite			
Copepod, *Acartia clausi*	S, U	Selenous acid	1,740	1,740	U.S. EPA, 1980
Copepod, *Acartia tonsa*	S, U	Selenous acid	800	800	U.S. EPA, 1980

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
Mysid shrimp (juvenile), *Mysidopsis bahia*	S, U	Selenous acid	600	600	U.S. EPA, 1978
Blue crab (adult), *Callinectes sapidus*	S, U	Sodium selenite	4,600	4,600	EG & G, Bionomics, 1978a
Dungeness crab, *Cancer magister*	S, U	Sodium selenite	1,040	1,040	Glickstein, 1978
Brown shrimp, *Penaeus aztecus*	S, U	Sodium selenite	1,200	1,200	EG & G, Bionomics, 1978b
Sheepshead minnow, *Cyprinodon variegatus*	S, U	Selenous acid	67,100	-	U.S. EPA, 1978
Sheepshead minnow, *Cyprinodon variegatus*	FT, M	Sodium selenite	7,400	7,400	EG & G, Bionomics, 1978d
Haddock (larvae), *Melanogrammus aeglefinus*	S, U	Selenous acid	599	599	U.S. EPA, 1980
Fourspine stickleback, *Apeltes quadracus*	S, U	Selenous acid	17,348	17,348	U.S. EPA, 1980
Pinfish, *Lagodon rhomboides*	S, U	Sodium selenite	4,400	4,400	EG & G, Bionomics, 1978c
Atlantic silverside, *Menidia menidia*	S, U	Selenous acid	9,725	9,725	U.S. EPA, 1980
Winter flounder (larvae), *Pseudopleuronectes americanus*	S, U	Selenous acid	15,069	-	U.S. EPA, 1980
Winter flounder (larvae) *Pseudopleuronectes americanus*	S, U	Selenous acid	14,245	14,651	U.S. EPA, 1980

Table 1. (Continued)

Species	Method*	Chemical	LC50/EC50 (µg/l)**	Species Mean Acute Value (µg/l)**	Reference
Summer flounder (embryo), *Paralichthys dentatus*	S, U	Selenous acid	3,497	3,497	U.S. EPA, 1980

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* S = static, FT = flow-through, U = unmeasured, M = measured

**Results are expressed as selenium, not as the compound.

Table 2. Chronic values for selenium

Species	Method*	Chemical	Limits (µg/l)**	Chronic Value (µg/l)**	Reference
		FRESHWATER SPECIES			
		Selenite			
Cladoceran, *Daphnia magna*	LC	Selenous acid	70-120	92	Kimball, Manuscript
Cladoceran, *Daphnia pulex*	LC	Sodium selenite	600-800	690	Reading, 1979
Rainbow trout, *Salmo gairdneri*	LC	Sodium selenite	60-130	88	Goettl & Davies, 1977
Fathead minnow, *Pimephales promelas*	ELS	Selenous acid	83-153	113	Kimball, Manuscript
		SALTWATER SPECIES			
		Selenite			
Sheepshead minnow, *Cyprinodon variegatus*	ELS	Selenous acid	470-970	675	U.S. EPA, 1978
Mysid shrimp, *Mysidopsis bahia*	LC	Selenous acid	127-143	135	U.S. EPA, 1978

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* LC = life cycle or partial life cycle, ELS = early life stage

**Results are expressed as selenium, not as the compound.

Acute-Chronic Ratios

Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
	Selenite		
Cladoceran, *Daphnia magna*	1,220	92	13

Table 2. (Continued)

	Acute-Chronic Ratios		
Species	Acute Value (µg/l)	Chronic Value (µg/l)	Ratio
Cladoceran, *Daphnia pulex*	3,870	690	5.6
Rainbow trout, *Salmo gairdneri*	12,500	88	142
Fathead minnow, *Pimephales promelas*	775	113	6.9
Mysid shrimp, *Mysidopsis bahia*	600	135	4.4
Sheepshead minnow, *Cyprinodon variegatus*	7,400	675	11

Table 3. Species mean acute values and acute-chronic ratios for selenium

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	FRESHWATER SPECIES		
	Selenite		
13	Midge, *Tanytarsus dissimilis*	42,400	-
12	Bluegill, *Lepomis macrochirus*	28,500	-
11	Goldfish, *Carassius auratus*	26,100	-
10	Snail, *Physa* sp.	24,100	-
9	Channel catfish, *Ictalurus punctatus*	13,600	-
8	Mosquitofish, *Gambusia affinis*	12,600	-
7	Brook trout, *Salvelinus fontinalis*	10,200	-
6	Rainbow trout, *Salmo gairdneri*	9,000	142
5	Flagfish, *Jordanella floridae*	6,500	-
4	Cladoceran, *Daphnia pulex*	3,870	5.6
3	Fathead minnow, *Pimephales promelas*	1,460	6.9
2	Cladoceran, *Daphnia magna*	710	13
1	Scud, *Hyalleia azteca*	340	-

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
	SALTWATER SPECIES		
	Selenite		
13	Fourspine stickleback, *Apeltes quadracus*	17,348	-
12	Winter flounder, *Pseudopleuronectes americanus*	14,651	-
11	Atlantic silverside, *Menidia menidia*	9,725	-
10	Sheepshead minnow, *Cyprinodon variegatus*	7,400	11
9	Blue crab, *Callinectes sapidus*	4,600	-
8	Pinfish, *Lagodon rhomboides*	4,400	-
7	Summer flounder, *Paralichthys dentatus*	3,497	-
6	Copepod, *Acartia clausi*	1,740	-
5	Brown shrimp, *Penaeus aztecus*	1,200	-
4	Dungeness crab, *Cancer magister*	1,040	-
3	Copepod, *Acartia tonsa*	800	-
2	Mysid shrimp, *Mysidopsis bahia*	600	4.4

Table 3. (Continued)

Rank*	Species	Species Mean Acute Value (µg/l)	Species Mean Acute-Chronic Ratio
1	Haddock, *Melanogrammus aeglefinus*	599	-

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* Ranked from least sensitive to most sensitive based on species mean acute value.

Freshwater Final Acute Value = 263 µg/l

Saltwater Final Acute Value = 406 µg/l

Final Acute-Chronic Ratio = 7.5 (ratio for the rainbow trout not used)

Freshwater Final Chronic Value = (263 µg/l)/7.5 = 35 µg/l

Saltwater Final Chronic Value = (406 µg/l)/7.5 = 54 µg/l

Table 4. Plant values for selenium

Species	Chemical	Effect	Result (µg/l)*	Reference
		FRESHWATER SPECIES		
		Selenite		
Alga (green), *Chlorella vulgaris*	not specified	Growth retardation	50	Hutchinson & Stokes, 1975
Alga (green), *Haematoccus cupensis*	not specified	Growth retardation	50	Hutchinson & Stokes, 1975
Alga (green), *Scenedesmus quadricauda*	Sodium selenite	Threshold toxicity	2,500	Bringman & Kuhn, 1959
Alga (blue-green), *Anabaena variabilis*	Sodium selenite	LC50	15,000**	Kumar & Prakash, 1971
Alga (blue-green), *Anacystis nidulans*	Sodium selenite	LC50	30,000**	Kumar & Prakash, 1971
		Selenate		
Alga (blue-green), *Anabaena variabilis*	Sodium selenate	LC50	17,000**	Kumar & Prakash, 1971
Alga (blue-green), *Anacystis nidulans*	Sodium selenate	LC50	40,000**	Kumar & Prakash, 1971
		SALTWATER SPECIES		
		Selenite		
Alga, *Skeletonema costatum*	Selenous acid	96-hr EC50 chlorophyll *a*	7,930	U.S. EPA, 1978
Alga, *Skeletonema costatum*	Selenous acid	96-hr EC50 Cell number	8,200	U.S. EPA, 1978

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* Results are expressed as selenium, not as the compound.

**Estimated from graph available in that publication.

Table 5. Residues for selenium

Species	Tissue	Chemical	Bioconcentration Factor	Duration (days)	Reference
		FRESHWATER SPECIES			
		Selenite			
Rainbow trout, *Salmo gairdneri*	muscle	Sodium selenite and selenite-75	15	48	Adams, 1976
Rainbow trout, *Salmo gairdneri*	whole body	Sodium selenite and selenite-75	78	48	Adams, 1976
Rainbow trout, *Salmo gairdneri*	whole body (estimate)	Sodium selenite	8	351	Hodson, et al. 1980
Fathead minnow, *Pimephales promelas*	muscle	Sodium selenite and selenite-75	18	96	Adams, 1976
Fathead minnow, *Pimephales promelas*	whole body	Sodium selenite and selenite-75	29	96	Adams, 1976
Bluegill, *Lepomis macrochirus*	whole body	Selenous acid	20	28	U.S. EPA, 1978

Table 6. Other data for selenium

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
		FRESHWATER SPECIES			
		Selenite			
Algae (diatoms), Mixed population	Sodium selenite	18 days	Growth inhibition	11,000	Patrick, et al. 1975
Cladoceran, *Daphnia magna*	Sodium selenite	24 hrs	LC50	16,000	Bringmann & Kuhn, 1977
Cladoceran, *Daphnia magna*	Sodium selenite	96 hrs	LC50	430	Halter, et al. 1980
Cladoceran, *Daphnia magna*	Sodium selenite	14 days	LC50	430	Halter, et al. 1980
Cladoceran, *Daphnia magna*	Selenous acid	48 hrs	LC50	1,200**	Kimball, Manuscript
Cladoceran, *Daphnia magna*	Selenous acid	48 hrs	LC50	1,200**	Kimball, Manuscript
Cladoceran, *Daphnia magna*	Selenous acid	28 days	LC50	240	Kimball, Manuscript
Scud, *Hyallela azteca*	Sodium selenite	14 days	LC50	70	Halter, et al. 1980
Coho salmon (fry), *Oncorhynchus kisutch*	Sodium selenite	43 days	LC50	160	Adams, 1976
Rainbow trout (fry), *Salmo gairdneri*	Sodium selenite	21 days	LC50	460	Adams, 1976
Rainbow trout (fry), *Salmo gairdneri*	Sodium selenite	21 days	Reduction in growth	250	Adams, 1976
Rainbow trout, *Salmo gairdneri*	Sodium selenite	48 days	LC50	500	Adams, 1976
Rainbow trout, *Salmo gairdneri*	Sodium selenite	96 days	LC50	290	Adams, 1976

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
Rainbow trout, *Salmo gairdneri*	Sodium selenite	9 days	LC50	5,400	Hodson, et al. 1980
Rainbow trout, *Salmo gairdneri*	Sodium selenite	9 days	LC50	6,900	Hodson, et al. 1980
Rainbow trout, *Salmo gairdneri*	Sodium selenite	9 days	LC50	7,000	Hodson, et al. 1980
Rainbow trout, *Salmo gairdneri*	Sodium selenite	41 days	Reduction of hatch of eyed embryos	47	Hodson, et al. 1980
Rainbow trout, *Salmo gairdneri*	Sodium selenite	50 wks	Blood iron decreased	53	Hodson, et al. 1980
Goldfish, *Carassius auratus*	Selenium dioxide	14 days	LC50	6,300	Cardwell, et al. 1976
Goldfish, *Carassius auratus*	Sodium selenite	10 days	Mortality	5,000	Ellis, et al. 1937
Goldfish, *Carassius auratus*	Sodium selenite	46 days	Gradual anorexia and mortality	2,000	Ellis, et al. 1937
Goldfish, *Carassius auratus*	Selenium dioxide	7 days	LC50	12,000	Weir & Hine, 1970
Goldfish, *Carassius auratus*	Selenium dioxide	48 hrs	Conditional avoidance	250	Weir & Hine, 1970
Fathead minnow, *Pimephales promelas*	Sodium selenite	48 days	LC50	1,100	Adams, 1976
Fathead minnow, *Pimephales promelas*	Selenium dioxide	9 days	LC50	2,100	Cardwell, et al. 1976
Fathead minnow, *Pimephales promelas*	Selenium dioxide	14 days	LC50	600	Halter, et al. 1980
Fathead minnow, *Pimephales promelas*	Selenous acid	8 days	LC50	400	Kimball, Manuscript

Table 6. (Continued)

Species	Chemical	Duration	Effect	Result (µg/l)*	Reference
Fathead minnow, *Pimephales promelas*	Selenous acid	8 days	LC50	430	Kimball, Manuscript
Creek chub, *Semotilus atromaculatus*	Selenium dioxide	48 hrs	Mortality	≥12,000	Kim, et al. 1977
Bluegill, *Lepomis macrochirus*	Sodium selenite	48 days	LC50	400	Adams, 1976
Bluegill, *Lepomis macrochirus*	Selenium dioxide	14 days	LC50	12,500	Cardwell, et al. 1976
		Selenate			
Fathead minnow, *Pimephales promelas*	Sodium selenate	48 days	LC50	2,000	Adams, 1976
		SALTWATER SPECIES			
		Selenite			
Pacific oyster, *Crassostrea gigas*	Sodium selenite	48 hrs	Development	>10,000	Glickstein, 1978
Pacific oyster, *Crassostrea gigas*	Selenium oxide	48 hrs	Development	>10,000	Glickstein, 1978

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* Results are expressed as selenium, not as the compound.

**Animals were fed during test.

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Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

The U.S. EPA (1975) reported that only one sample out of 418 analyzed for Interstate Carrier Water Supplies in 1975 exceeded the drinking water limit for selenium of 10 µg/l. According to Craun, et al. (1977), a study of home tap water samples collected from 3,676 residences located in 35 geographically dispersed areas found only 9.96 percent of the samples with selenium levels above the detection limit of 1 µg/l. The average, minimum, and maximum of the mean selenium levels detected in the 35 areas were 3.82 µg/l, 1.0 µg/l, and 36.8 µg/l, respectively.

Smith and Westfall (1937) found measurable amounts (50 to 330 µg/l) of selenium in drinking waters from 10 of 44 wells in a seleniferous area of South Dakota. In three Oregon counties, Hadjimarkas (1965) found averages of 2 µg/l or less for 21, 23, and 28 farm samples.

Ingestion from Food

Selenium concentrations in plants depend largely on the concentration and availability of selenium in the soil where the plants are grown. For example, in South Dakota, whole milk may contain up to 1,200 µg/l of selenium, whole eggs as much as 10 µg/g of selenium, and vegetables (string beans, lettuce, turnip leaves, and cabbage) from 2 to 100 µg/g [National Academy of Sciences (NAS), 1977].

A number of investigators have found samples of wheat and wheat products that contain 1 to 4 µg/g of selenium (Lakin and Byers, 1941; Robinson, 1936).

Additional information on selenium levels in food are shown in Tables 1 to 4. Table 1 lists the selenium content of staple foods of the American

TABLE 1

Selenium Content of Some Foods in the American Diet*

Food	Average Selenium Content µg/g (wet wt.)
Vegetables, canned and fresh[a]	0.010 (0.004–0.039)
Fresh garlic	0.249
Mushrooms, canned and fresh	0.118
Fruits, canned and fresh	0.006 (<0.002–0.013)
Cereal products[b]	0.387 (0.0266–0.665)
Corn flakes	0.026
Rice cereal	0.028
Egg white	0.051
Egg yolk	0.183
Brown sugar	0.011
White sugar	0.003
Cheeses	0.082 (0.052–0.105)
Table cream	0.006
Whole milk	0.012
Meat (excluding kidney)	0.224 (0.116–0.432)
Seafood	0.532 (0.337–0.658)

*Source: Morris and Levander, 1970

[a] Mean excluding mushroom and garlic

[b] Mean excluding corn flakes and rice cereal

diet (Morris and Levander, 1970). The relationship of selenium levels in foods grown in seleniferous and nonseleniferous soils is in Table 2. Several estimates on the average daily intake of selenium by humans are presented in Table 3, while Table 4 reports the estimated daily intake of a 6-month-old infant.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. An appropriate BCF can be used with data concerning food intake to calculate the amount of selenium which might be ingested from the consumption of fish and shellfish. An analysis (U.S. EPA, 1980) of data from a food survey was used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish is 6.5 g/day (Stephan, 1980). Adams (1976) obtained BCF values of 15 and 18 for selenium and muscle of rainbow trout and fathead minnows, respectively. For lack of other information, a value of 16 can be used as the weighted average bioconcentration factor for selenium and the edible portion of all freshwater and estuarine aquatic organisms consumed by Americans.

Tests on the bioconcentration of selenium by aquatic animals have only been conducted with three species of freshwater fish. The tests with rainbow trout and fathead minnows (Adams, 1976) gave BCF values of 15 and 18, respectively, for the whole body. The test with the bluegill (U.S. EPA, 1978) lasted 28 days and gave a BCF of 20 for whole body. Based on data for lead and cadmium, selenium would probably have a lower BCF for fish and decapod muscle than for fish whole body, but probably would have a higher BCF for molluscs.

TABLE 2

Selenium Content of Seleniferous vs. Nonseleniferous Vegetables (μg Se/gram, wet weight)

Product	Nonseleniferous[a] Morris and Levander (1970)	Seleniferous[b] Smith and Westfall (1937)
Potato	0.005	0.940
Tomato	0.005	1.22
Carrots	0.022	1.30
Cabbage	0.022	4.52
Onion	0.015	17.8

[a] Samples were purchased in the Beltsville, Maryland area from local food stores. Brand name products were selected whenever possible.

[b] Samples of foodstuffs used by the people living in four seleniferous counties (Tyman, Tripp, and Gregory in South Dakota and Boyd in Nebraska) were collected and analyzed for selenium content.

TABLE 3

Estimated Human Daily Intake of Selenium from Dietary Sources
(μg/day)

Food	New Zealand[a]	U.S.A. Maryland	Canada[a] Ontario	Canada[b] Toronto	Canada[b] Toronto	Canada[b] Winnipeg	Canada[b] Halifax	Japan[c]
Plant								
Vegetables Fruit, sugars	5.8	5.4	6.9	5.1	1.3	9.1	7.4	6.5
Cereals	4.3	44.5	74.4	62.0	111.8	79.8	105.0	23.9
Animal								
Dairy products	8.4	13.5	23.4	6.5	5.0	27.6	21.8	2.3
Meat, fish	37.7	68.6	46.0	24.7	30.4	64.3	90.0	55.6
Totals	56.2	132.0	150.7	98.3	148.5	190.8	224.2	88.3

[a] Watkinson, 1974

[b] Thomson, et al. 1975

[c] Sakurai and Tsuchiya, 1975

TABLE 4

Estimated Infant Daily Intake of Selenium From Dietary Sources (6-month-old, 15-pound child)*

Food	Daily Consumption grams	ug Se/gram	Daily Intake ug Se
Milk	824	0.013[a]	11
Orange	122	0.014[a]	2
Dry Mixed Cereal	10	0.540[b]	5
Egg Yolk	17	0.437[a]	7
Strained Meat	28	0.097[a]	3
Strained Fruit	57	0.002[a]	--
Strained Vegetable	57	0.003[a]	--
Total Selenium Intake			28

*Source: Levander, 1976

[a] Average of Morris and Levander (1970) and Arthur (1972)
[b] Arthur, 1972

Inhalation

Zoller and Reamer (1976) reported that most urban regions have atmospheric particulate selenium concentrations ranging from 0.1 to 10 ng/m^3. Air samples collected at Cambridge, Mass. averaged 1 ng/m^3 of selenium (Hashimoto and Winchester, 1967), while Dams, et al. (1970) found selenium values of 2.5 ng/m^3 at Niles, Mich. and 3.8 ng/m^3 at East Chicago, Ind.

Eighteen air samples collected around Buffalo, N.Y. during 1968-1969 had selenium levels ranging between 3.7 and 9.7 ng/m^3, with an average of 6.1 ng/m^3 (Pillay, et al. 1971).

Dermal

Selenium has a large number of industrial uses, and most dermal exposures of significance would be primarily confined to occupational settings. Dermatitis has been observed on the hands of workers handling elemental selenium (Amor and Pringle, 1945). Selenium dioxide has also caused dermatitis (Pringle, 1942) and burns when in contact with the eyes (Middleton, 1947). When allowed to penetrate below the fingernails, selenium dioxide has caused painful inflammatory reaction (Glover, 1954).

Some antidandruff shampoos contain 1 to 2.5 percent selenium sulfide or selenium disulfide (Cummins and Kimura, 1971; Orentreich and Berger, 1964; NAS, 1976). Cummins and Kimura (1971) described an unpublished study which showed that ordinary application of a shampoo containing one percent selenium sulfide for one year did not result in a significant elevation of selenium levels in the blood when compared with controls. The authors concluded that no apparent percutaneous absorption of selenium occurred following one year of age.

PHARMACOKINETICS

Absorption

Thomson and Stewart (1973) conducted a study in female Wistar rats to estimate gastrointestinal absorption rates for selenite and selenomethionine. Two groups of 20 rats received a measured dose of approximately 5 µCi (^{75}Se) selenomethionine containing not more than 5 µg Se, one group by intravenous injection, and the other by intragastric intubation. Another two groups of 20 rats received intravenous or oral doses of (^{75}Se) selenite, again containing not more than 5 µg Se. Three methods were employed for estimating intestinal absorption yielding a percentage range of 91 to 93 and 95 to 97 for selenite and selenomethionine, respectively.

In a subsequent study, Thomson, et al. (1975) estimated the intestinal absorption of selenocystine and selenomethionine for two groups of 25 female Wistar rats. The method of exposure was gastric intubation, and the dose levels were approximately 5 µCi of (^{75}Se) selenocystine and approximately 2 µCi of (^{75}Se) selenomethionine. Each dose contained not more than 5 µg Se. Estimated absorption of (^{75}Se) selenocystine was 81.1 percent of the administered dose and that of (^{75}Se) selenomethionine was 86.4 percent of the dose.

Thomson and Stewart (1974) have also investigated gastrointestinal absorption rates in three young women aged 33, 21, and 25 years, respectively. The mean height and weight were 1.60 m and 57 kg, respectively. While fasting, each received a measured oral dose of approximately 10 µCi (^{75}Se) selenite containing not more than 10 µg Se. Calculated intestinal absorption rates for the three women were 70, 64, and 44 percent of the administered dose.

The literature contains practically no quantitative data on the pulmonary absorption of gaseous or finely dispersed particulate selenium compounds (NAS, 1976). For purposes of extrapolating air standards to drinking water standards, Stokinger and Woodward (1958) assume that both the pulmonary and gastrointestinal absorptive factors are 80 percent of appropriately administered doses.

Little quantitative information is available concerning the dermal absorption of selenium compounds (NAS, 1976).

Distribution

Dudley (1936) investigated the distribution of selenium in domestic farm animals fed sodium selenite or selenium-bearing plants. A hog, calf, and sheep were fed sufficient selenium (19.64 mg/kg, 20 mg/kg, 11.21 mg/kg for the hog, calf, and sheep, respectively) to induce prompt fatal outcome within 6 hours to 3 days. For the hog, sheep, and calf the level of selenium in the blood amounted to 5, 7, and 27 ug/ml, respectively. The tissues with the highest selenium levels were the liver, kidney, and spleen. The heart, lungs, brain, and muscle of the three species contained lesser amounts of the element.

Handreck and Godwin (1970) introduced a ^{75}Se-labeled pellet (1.0 g elemental selenium and 0.25 mCi activity) into the rumen of each of eight sheep (four raised on selenium adequate diets and four on selenium deficient diets) and monitored them in metabolism cages for a period of 1 month prior to sacrifice. ^{75}Selenium was detected in every tissue examined. The highest levels were found in kidney cortex and medulla, liver, and various glandular tissues. Lowest levels were found in fat, bile, grey marrow, and parts of the eye. Initial selenium status of the animals had little effect on the resulting overall distribution.

Kincaid, et al. (1977) investigated the distribution of selenium in three groups of five male Holstein calves, approximately 120 days old and 105 kg, fed a practical diet (containing 0.3 μg/g Se) supplemented with 0, 0.1, or 1.0 μg/g added selenium, as sodium selenite. After 28 days on the experimental diets, the calves were orally dosed with 608 uCi ^{75}Se (specific activity 93 mCi/mg Selenium) via gelatin tablets. The calves were sacrificed 48 hours after dosing. The general effect of the supplemental dietary selenium on tissue ^{75}Se uptake of an oral ^{75}Se dose is reflected by the blood data. Blood ^{75}Se concentrations were reduced about 15 and 35 percent with 0.1 μg/l and 1.0 μg/g added dietary selenium, respectively. The kidney, the middle and lower small intestine, and the liver retained the greatest amounts of ^{75}Se for all groups.

Using information collected for 94 pigs included in a Canadian Government supported study of the effects of dietary copper supplementation, Young, et al. (1977) have investigated the statistical relationships between dietary selenium (0.06 to 0.61 μg/g dry matter) and liver selenium (0.93 to 2.76 μg/g dry matter) and longissimus muscle selenium (0.38 to 1.84 μg/g dry matter). The resultant estimation equations are as follows:

$$\text{Liver Se} = 0.971 + 5.79 \text{ Diet Se} - 4.74 \text{ Diet Se}^2,\ R^2 = 51.5$$

$$\text{Muscle Se} = 0.154 + 5.264 \text{ Diet Se} - 4.526 \text{ Diet Se},\ R^2 = 63.3.$$

In summary, the primary deposition sites for selenium in the body are the liver, kidney, spleen, and middle and lower sections of the small intestine followed by the heart, lungs, brain, and muscle. Based on the work of

Kincaid, et al. (1977), it is apparent that actual tissue concentration levels are affected both by dose level and levels in the normal diet, but the primary deposition sites remain the same.

Metabolism

The National Academy of Sciences (1977) at the request of, and funded by, the U.S. EPA under contract no. 68-01-3139 has thoroughly summarized and reviewed the literature concerning the biotransformation aspects of selenium metabolism. Hence, the material in this section is quoted from that review.

> Little is known about the biochemistry of selenium in mammalian systems. At concentrations required nutritionally, selenium is incorporated into specific functional proteins; at higher concentrations, it is incorporated into molecules normally served by sulfur. Selenium analogs are often less stable than sulfur compounds, and this lability may be the basis of toxicity. Selenium biochemistry has been the subject of recent reviews (Stadtman, 1974).
>
> By the mechanism used for sulfate ion, microorganisms are capable of activating selenate with adenosine triphosphate (Wilson and Bandurski, 1956), but it is not clear that appreciable amounts of activated selenate are reduced to selenite via 3'-phosphoadenosine-5'-phosphoselenate, which would be directly analogous to the recognized reduction of activated sulfate to sulfite by phosphoadenosine phosphosulfate. In animals, phosphoadenosine phosphosulfate is important in the formation of sulfate esters in the detoxication of foreign compounds and the metabolism of steroids and other indigenous compounds (Lipmann, 1958). The activity of 3'- phosphoadenosine-5'-phosphoselenate, if formed, in the formation of selenate esters, is not known. Although selenate and selenite ions are absorbed and incorporated into organic molecules as selenide, it is not fully known how the reduction of selenium is accomplished (Stadtman, 1974).
>
> Selenite is methylated by mammalian tissues in an apparent detoxication process. Mouse liver and kidneys use S-adenosylmethionine and reduced glutathione to form dimethylselenide from selenite (Ganther, 1966); the lungs are also active in the methylation, but muscle, spleen, and heart have little activity. Dimethylselenide is less toxic than sodium selenite (McConnell and Portman, 1952).
>
> Selenite and selenate are metabolized to trimethylselenonium ion, $(CH_3)_3Se^+$, which is the principal excretory product of selenium in urine (30 to 50 percent of the urinary selenium) (Byard, 1968; Palmer, et al. 1969; Palmer and Olson, 1974).

Again, trimethylselenonium ions are less toxic than selenite or selenate ions (Obermeyer, et al. 1971). Although these methylated products are less toxic than the parent selenium compounds, they are involved by unknown mechanisms in synergistic toxicity; dimethylselenide and mercury toxicities are synergistic (Parizek, et al. 1971), as are those of trimethylselenonium ion and arsenic (Obermeyer, et al. 1971).

In mammalian systems, inorganic selenium usually is not incorporated into amino acids (Cummins and Martin, 1967), although there is some evidence of the incorporation of selenium from sodium selenite into a rabbit protein (Godwin and Fuss, 1972). The matter is confusing, because inorganic selenium can be reduced to complex with disulfides to give selenodisulfides (R-S-Se-S-R), as is the case with two molecules of cysteine (Painter, 1941; Ganther, 1968) or reduced glutathione (Ganther, 1971).

Selenium appears to serve as an essential element in some oxidation-reduction processes in mammals. Sheep skeletal muscles contain a small selenoprotein (mol. wt., 10,000) that has a heme group. Although the selenium appears to be an integral part of the protein, its position and function in the protein are not known (Pedersen, et al. 1973).

A second selenoprotein is known: glutathione peroxidase, an enzyme, catalyzes the reduction of hydrogen peroxide. The activity of glutathione peroxidase in red cells of selenium deficient animals is low, but may be restored specifically by selenium administration (Rotruck, et al. 1973). The enzyme has a molecular weight of 84,000 and is composed of four subunits of molecular weight 21,000 each; each subunit contains one atom of selenium (Flohe, et al. 1973).

Excretion

Rosenfeld (1964) has investigated the effects of mode and frequency of selenium administration on urinary, fecal, and respiratory excretion rates in male and female Sprague-Dawley rats (weight of females 200-300 g; weight of males 300-450 g). After a single tracer dose of 7.5 μg of ^{75}Se, the percent of administered dose excreted in 24 hours in the urine and feces for each mode of administration are: subcutaneous, 12.9 and 3.7 percent; intraperitoneal 26.0 and 4.0 percent; and intragastric, 34.0 and 13.9 percent. For tracer doses it does not appear that repeated administration (by various routes) alters the total elimination pattern observed after a single dose, but the amount excreted by the kidney, gut, and lung show some differences.

The primary mode of elimination for tracer doses is the urinary tract. Forty percent of the injected dose is excreted in the urine, and about one-half or less is excreted by the gastrointestinal tract and lung. Selenium was eliminated by the urinary, gastrointestinal, and respiratory tracts up to 150 days. Respiratory elimination ceased 3 days after subcutaneous injections. Administration of repeated subacute doses (2.5 mg of selenium (H_2SeO_3)/kg mixed with ^{75}Se ($H_2{}^{75}SeO_3$) resulted in a reversal of the route of elimination as indicated by the decreased rate of urinary excretion and increased excretion of ^{75}Se in the feces and by the lung.

Thomson and Stewart (1973) and Thomson, et al. (1975) have determined urinary and fecal excretion rates for Wistar rats exposed to (^{75}Se) selenocystine, (^{75}Se) selenomethionine, and (^{75}Se) selenite by oral administration. Two groups of 12 female rats bred from the same colony and initially weighing 90 to 120 g were maintained on tap water and a pelleted stock diet containing 180 g available protein and 0.025 mg Se/kg. The rats in one of the groups were anaesthetized with 5 mg sodium pentobarbitone (pentobarbital) and given by gastric intubation a known amount (approximately 5 µCi) of (^{75}Se) selenocystine. The same procedure was used to administer a known amount (approximately 2 µCi) of (^{75}Se) selenomethionine to the second group. Two groups of 12 female rats, initially weighing 140 to 160 g, were exposed by the same procedures to 5 µCi (^{75}Se) selenomethionine and (^{75}Se) selenite, respectively. None of the single dose levels for the four groups contained more than 5 µg Se. After exposure the rats were placed in metabolic cages for the separate collection of urine and feces. These collections were completed at 24-hour intervals for 7 days.

The percentages of administered doses excreted (during the first week after the oral dose) in the urine and feces for each set of animals are as follows:

	Urine	Total Fecal
(^{75}Se) Selenocystine (5 μCi)	11.4	27.1
(^{75}Se) Selenomethionine (2 μCi)	5.0	22.2
(^{75}Se) Selenomethionine (5 μCi)	4.2	15.6
(^{75}Se) Sodium selenite	12.7	20.6

The relationships between selenium dose and that excreted in the respiratory gases have been researched by McConnell and Roth (1965). Young adult male rats were injected subcutaneously with a single dose of selenium either as selenite ($^{75}SeO_3$) or L-seleno-75 methionine to which was added amounts of the correspondent stable selenium compound. The doses of selenite ranged from 0.005 to 5.410 mg/kg with corresponding ranges of 24-hour excretion for exhaled air and urine of 0.2 to 52 percent and 32.9 to 1.9 percent, respectively. The single dose levels for L-seleno-75- methionine ranged from 0.001 to 5.583 mg/kg with corresponding exhaled air and urine excretion percentages of 1.3 to 35.9 and 27.10 to 6.82, respectively.

Selenium excretion as a percent of administered dose had also been studied in humans (Waterlow, et al. 1969; Thomson and Stewart, 1974). Waterlow, et al. (1969) gave each of eight infants a single dose of 0.1 μCi (^{75}Se) methionine/kg body weight (six infants received oral dose and two intravenous); the human subjects were male infants, aged 7 to 16 months, admitted to the hospital with severe malnutrition. All but one of the infants were on a high protein diet (3 to 5 g/kg/day) at the time when the study began. Forty-eight-hour excretion levels were reported for only three of the six infants that received oral doses and for both intravenous exposed infants; the 24-hour instead of the 48-hour excretion level was reported for one of the infants, and nothing was presented for the other two infants. Ranges of 48-hour urinary and fecal excretion percentages are: oral (3.2 to 7.25 for urine and 3.6 to 15.15 for feces); and intravenous (8.6 to 8.95 for urine and 1.7 to 2.95 for feces). The 24-hour excretion percentages of the one orally exposed infant are 4.5 for urine and 8.1 for feces. When selenomethionine was given by mouth, during the first 48 hours more radioactivity was lost in the feces than the urine. When the isotope was given by vein, the greater part of the loss occurred in the urine. In the subjects that received selenomethionine orally, the loss in the feces tended to remain higher than that in the urine for about the first 10 days. However, the fecal loss, expressed as percent of retained dose per day, declined as time went on, whereas the rate of loss in the urine remained rather constant.

Thomson and Stewart (1974) studied selenium excretion by feeding three women aged 33, 20, and 25 years (mean height of 1.60 meters and weight of 57 kg) an oral dose of approximately 10 μCi (^{75}Se) selenite containing not more than 10 μg Se; the women were fasting at the time of administration. In the first 24 hours after the dose of ^{75}Se, urine was collected every hour for 10 hours, then every 2 hours for 6 hours and finally at the end of 8 hours. Subsequently, 24 collections were made daily for the next 13 days. A gelatin capsule containing 50 mg brilliant blue marker and 200 mg methyl cellulose was swallowed immediately after the ^{75}Se dose. All individual stools for at least 14 days were collected separately. Thereafter, a single fecal sample was obtained each week on the day of the urine collection. Expired air from each subject was collected in Douglas bags for 8 to 10 minute periods at regular time intervals during the first nine hours. Dermal loss was measured by analysis of underclothing. Urine and fecal excretion, expressed as a percent of dose, for the first two weeks were 7 to 14, and 58 to 33, respectively. No radioactivity was detected in the Douglas bags containing expired air. However, on day one, traces of ^{75}Se of less than 0.02 percent of the dose were found in the HNO_3 and mercuric chloride solutions through which expired air had been passed, but there was no ^{75}Se in the air collected on day two. No radioactivity was detected in the underclothing worn during the first, second, or third day.

Based on these studies, it is apparent that the primary routes of excretion are in the urine and feces and that the distribution between the two depends on the level of exposure and length of time subsequent to exposure.

EFFECTS

Acute, Subacute, and Chronic Toxicity

The toxic effects of selenium have been recognized much longer than the nutritional ones. In the 1930s, it was discovered that certain geographical areas are seleniferous and produce plants with high selenium content. In addition to the generalized increase of selenium in vegetation from such areas, a few species of plants were identified that thrived there and were termed selenium indicator plants (Rosenfeld and Beath, 1964). These plants characteristically accumulate extremely high levels of selenium in the form of nonprotein selenoamino acids such as Se-methylselenocysteine and produce acute toxicity in animals consuming them (Burk, 1976)

The diseases of "blind staggers" and "alkali disease" in cattle are selenium toxicosis and have been described by many observers. The mechanism of toxic action is not completely agreed upon (Browning, 1969).

Selenium deficiencies also occur in livestock with equally debilitating results. "White muscle" disease (a selenium-Vitamin E deficiency) occurs in dams and young animals.

Blind staggers is the name applied to the acute form of selenium disease. Though the animal is not blind and may not stagger, there is some impairment of vision, a difficulty in judging near objects, and a general tendency to wander. Paralysis and evidence of abdominal pain occur in the final states of the disease; death is due to respiratory failure (Browning, 1969).

Alkali disease is a more chronic form of selenium poisoning of livestock than blind staggers. Primary symptoms are emaciation, lack of vitality, loss of hair from the mane and tail of horses and from the switch of cattle, and in severe cases separation of the hoof. Lambs are born with abnormal eyes, deformed feet, and myopathies. Lesions of internal organs are more marked in the heart (atrophy and decompensation) and liver (cirrhosis). The kidneys may show glomerulonephritis and erosion may occur in the joints of the long bones erosion. There is also a high incidence of anemia (Browning, 1969).

Acute selenium poisoning in laboratory animals has been produced by a toxic dose of selenium compound administered orally, subcutaneously, intraperitoneally, or intravenously. Sodium selenite and selenate are the most commonly tested selenium salts. The lethal dose has varied according to different observers, owing probably to species differences, age of the animals, mode of administration, and the purity of the salts (Fishbein, 1977). Table 5 summarizes some of the data reported in the literature on the acute toxicity of various selenium compounds.

Navia, et al. (1968) investigated the cariostatic activity of 4 ppm selenium (as Na_2SeO_3) in two groups of rats by administering it in either the drinking water or in a purified, caries-producing diet. Selenium was shown to cause sulcal lesions and a significant decrease in food intake in the groups given 4 ppm selenium in the water.

TABLE 5

Acute Toxicity of Some Selenium Compounds*

Compound	Experimental Animal	Mode of Administration	Toxicity	Reference
Sodium selenite	Rat	Intraperitoneal injection	MLD^{b,d,g}-3.50 3.25 mg Se/kg body wt	Franke and Moxon, 1936
	Rat	Intravenous injection	MLD^{c,g} 3 mg Se/kg body wt	Smith and Westfall, 1937
	Rabbit	Intravenous injection	MLD^{c,g} 1.5 mg Se/kg body wt	Smith and Westfall, 1937
	Rat	Injection	MLD^{d,g} 3-5.7 mg Se/kg body wt	Moxon and Rhian, 1943
	Rabbit	Injection	MLD^{d,g} 0.9-1.5 mg Se/kg body wt	Moxon and Rhian, 1943
	Dog	Intraperitoneal injection	MLD^{d,g} 2.0 mg Se/kg body wt	Moxon and Rhian, 1943
Sodium selenate	Rat	Intraperitoneal injection	MLD^{b,g} 5.25-5.75 mg Se/kg body wt	Franke and Moxon, 1936
	Rat	Intravenous injection	MLD^{c,g} 3 mg Se/kg body wt	Smith and Westfall, 1937
	Rabbit	Application to skin	839 mg of compound caused death in 5 hr; 49 mg caused death in 24 hr.	Dudley, 1938
Hydrogen selenide	Rat	In air	All animals exposed to 0.02 mg/liter to air for 69 min. died within 25 days	Dudley, 1938
DL-selenocystine	Rat	Intraperitoneal injection	MLD^{a,b,g} 4.0 mg Se/kg body wt	Moxon, 1940
DL-selenomethionine	Rat	Intraperitoneal injection	MLD^{a,g} 4.25 mg Se/kg body wt	Klug, et al. 1949
Diselenodipropionic	Rat	Intraperitoneal injection	LD$_{50}$ 9 25030 mg Se/kg body wt	Moxon, 1938
Dimethyl selenide	Rat	Intraperitoneal injection	LD$_{50}$ ^{e,g} 1,600 mg/kg body wt	McConnell and Portman, 1952
Trimethylselenonium chloride	Rat	Intraperitoneal injection	LD$_{50}$ ^{b,g} 49.4 mg Se/kg body wt	Obermeyer, et al. 1971

*Source: National Academy of Sciences, 1976

Although the possibility exists that range animals and man may be exposed to sufficient selenium to result in acute effects, the problem of acute toxicity seems less important than that of chronic toxicity (NAS, 1976).

The concentrations of selenium in the diet, or given orally, leading to selenium poisoning (selenosis), depend on the chemical form of selenium and other dietary components (Fishbein, 1977). In general, however, the concentration necessary to produce chronic selenium poisoning has been observed in rats and dogs at dietary levels of 5 to 10 µg/g (Anspaug and Robison, 1971). Chronic effects from prolonged feeding with diets containing added selenium in amounts of 5 to 15 µg/g include liver damage in the form of atrophy, necrosis, cirrhosis, hemorrhage, and marked and progressive anemia with very low hemoglobin values in some species (Fishbein, 1977). Vesce (1974) noted changes in endocrine glands, and especially the ovaries, pituitary, and adrenals following oral administration of 5 to 12.5 mg sodium selenide to guinea pigs over two periods of 20 days.

The National Academy of Sciences (1976) has thoroughly summarized and reviewed the literature concerning selenium toxicity in an attempt to establish a "no effect" dose level for the element. Their summary is quoted here.

> In 1967, Tinsley, et al. (1967) concluded that, so far as longevity is concerned, a daily dose of 0.5 mg of selenium as selenite or selenate per kilogram of body weight per day seemed to be the threshold dose in rats on a casein-Cerelose diet (for a 200 g rat eating 10 g of feed per day, this would be the equivalent of 10 µg/g). On the other hand, a calculated maximum body weight was reported to be decreased by as little as 0.5 µg/g of selenium. In addition, Harr, et al. (1967) reported that when additions of 0.5-2 µg/g of selenium were made to the diets, proliferation of the hepatic parenchyma was more prevalent than in control animals on diets with no added selenium and that selenium added to a commercial diet produced less toxicity than selenium added to a casein-Cerelose diet.
>
> A complementary report gives detailed data (Bioassay of Selenium Compounds for Carcinogenesis in Rats, 1966). Here again, the

weight effects were noted. However, a careful study of the data on chronic liver and bile duct hyperplasia shows that this lesion was even more prevalent in a commercial diet without added selenium than in a casein-Cerelose diet with 0.5 ug/g of added selenium. This may mean that the hyperplasia does not indicate a toxic effect of the element. In a later report, Harr and Muth (1972) state, with reference to the studies of the semipurified diet, that the minimum toxic level for liver lesions was 0.25 ug/g. With reference to longevity and lesions in heart, kidneys, and spleen, they concluded that the minimum toxic level was 0.75 ug/g. They state, however, that rats fed 0.5 ug/g of selenium in the diet grew as well as the controls. They concluded that the estimated dietary threshold for physiologic-pathologic effect is 0.4 ug/g and for pathologic-clinical effects, 3 ug/g. Neither growth nor longevity was adversely affected by as much as 2.5 ug/g of added selenium in a torula yeast diet to which the carcinogen fluorenylacetamide had been added. The physiologic significance of some of the observations of this group is difficult to evaluate.

Pletnikova (1970) has recommended a maximum concentration of 0.001 mg of selenium as selenite or selenate per liter of water for Russian drinking water. She reports 0.01 mg/liter as the threshold for detection by odor. She also reports decreased liver function and effects on the activities of some enzymes along with increased blood glutathione in rats receiving 0.5 ug of selenium per kilogram of body weight per day (about 0.01 mg/liter) for a period of six months. These effects were not obtained at a level of one-tenth of this amount. Unfortunately, she does not describe the diet or state its selenium content. Quite likely, the selenium intake from it was considerably greater than that from the water containing 0.01 mg/liter. Further, bromsulfophthalein (BSP) clearance was used for the liver-function test. With this, BSP is excreted into the bile conjugated with reduced glutathione (GSH). If selenium catalyzes GSH oxidation, the GSH pool available to react with the dye would be depleted; hence, the effect may not indicate a toxicity. The physiologic significance of the observations made in this study is not clear.

Palmer and Olson (1974) studied the toxicity of selenite and selenate to rats on corn or rye-based diets. They administered selenite or selenate in water at the rate of 2 or 3 mg/l for a period of six weeks. Each form produced a small reduction in rate of gain without mortality. Earlier, Schroeder and Mitchener (1971) reported severe toxicity at the 2 mg/l level for selenite selenium but not for selenate selenium.

Halverson, et al. (1966) fed postweanling rats for 6 weeks on wheat diets containing 1.6, 3.2, 4.8, 6.4, 8.0, 9.6, or 11.2 ug/g of naturally occurring or selenite selenium. Growth was not affected below the 4.8 ug/g level of selenite or the 6.4 ug/g level of selenium from grain. At 6.4 ug/g of selenium or above, restriction of feed intake, increased mortality, increased spleen weight and size, increased pancreas size, reduced liver weight, body weight ratios, and reduced blood hemoglobin were noted.

These effects were not observed in rats on diets containing lesser amounts of selenium.

Thapar, et al. (1969) found that 8 µg/g of selenium added as selenite to either a practical corn-soy diet or a Cerelose-soybean protein diet reduced egg production, weight and hatchability of eggs, body weight, survival rate, and growth of progeny of laying hens fed the diet from 1 day of age for as long as 105 weeks. But no detrimental effects were observed when selenium was added at the rate of 2 µg/g, and it is possible that this addition improved the levability of hens on the Cerelose-soybean protein diet. Similar findings were later reported by Arnold, et al. (1973). Much earlier, Poley, et al. (1941) reported that 2 µg/g of selenium from grain improves the growth of chicks on a practical-type diet.

Witting and Horwitt (1964) reported that growth curves had shown that the selenium requirement of the tocopherol-deficient rat has a very narrow optimal range. The best growth rate was obtained on the addition of 0.1 µg/g of selenium as selenite. At 0.3 µg/g of selenium, the growth was better than at 0.03 µg/g, but not as good as at 0.1 µg/g. With the diet severely deficient in vitamin E, selenium toxicity was noted at what these authors considered an unusually low level of the element: 0.25 µg/g in the basal diet plus 1 µg/g as selenite.

Obviously the chronic toxicity of selenium will depend on the criteria used to determine the "no-effect" dose level. For the normal diet, 4 to 5 µg/g will usually inhibit growth, and this may be the best indicator of toxicity. In a diet deficient in vitamin E, 1 µg/g may be toxic. During the development of teeth, 1 to 2 µg/g may be toxic if subsequent cariogenesis is used to measure toxicity. Histopathologic observations may suggest that less than 1 µg/g can be toxic. However, the physiologic significance of the observations may not be clear, and the same may be said for biochemical parameters indicating that even lower levels can be toxic. In many areas, livestock are regularly fed diets containing over 0.5 µg/g of the element, and there has been nothing to suggest that they fare less well than animals on diets of lower selenium content.

Information concerning the effects of selenium poisoning in humans has been obtained from epidemiologic studies of persons who live in seleniferous areas and consume locally produced food and drink and from studies of occupationally related selenium exposures.

Shapiro (1973) has prepared an excellent review of selenium toxicity studies in humans. Only some of the salient features of this report will be mentioned here.

Water supplies, even in seleniferous areas of the western United States have not generally been considered a potential source of selenium toxicity in man. However, elevated levels have been found in a few isolated areas. One instance of toxicity, due to selenium contained in an underground water source, was described by Beath (1962). Well water from the Wasatch geological formation in Utah contained 9 mg/l selenium. Chronic selenosis occurred in humans and in one animal drinking the water. No selenium was found in the food. Lassitude, total or partial loss of hair, discoloration, and loss of fingernails were symptoms of the condition. A halt in the use of the water brought regrowth of the hair and nails and increased mental alertness.

A systematic epidemiological study by Smith, et al. (1936) of chronic toxicity of selenium in man was carried out in South Dakota, Wyoming, and Nebraska on farms where animals were known to be suffering from "alkali disease." A number of clinical signs in farm workers were attributed to selenium toxicosis, notably bad teeth, jaundice, chloasma, vertigo, chronic gastrointestinal disease, dermatitis, nail changes, arthritis, edema, lassitude, and fatigue. Analyses were made of the selenium content of the food of these people, and daily selenium intakes of 0.1 to 0.2 mg of selenium per kilogram of body weight were recorded. Nearly all the urine samples tested contained measurable amounts of selenium, and 45 percent of these contained from 0.2 to 1.33 μg/ml.

There was some correlation between the symptoms of selenosis and a urinary content greater than 0.2 μg/ml. In reviewing these findings, Shapiro (1973) states: "These studies suggest, but do not firmly establish, that chronic selenium toxicity of dietary origin exists in man." Only when blood and tissue levels are measured in affected individuals, however, will such conclusions be valid.

For many years, hunters in South America have realized that ingestion of fruit of the monkey pod tree Lecythis ollaria could lead to nausea, vomiting, and generalized hair loss (Kerdel-Vegas, et al. 1965). The toxic compound has recently been isolated and identified as selenocystathionine (Aronow and Kerdel-Vegas, 1965).

Carter (1966) reported the death of a child resulting from the ingestion of gun-bluing compound containing 1.8 percent selenious acid. In this case, which is the only autopsy report describing the histopathology of acute selenium poisoning, there was fulminating peripheral vascular collapse, pulmonary edema, and coma. At autopsy the gastric mucosa was a brick-red color, and marked intestinal vascular congestion was observed. Garlic odor of the breath was present before death but was not detected in post mortem examination of the various organs. The lungs were diffusely hemorrhagic, congested, and edematous, but no specific renal or hepatic necrosis was described. Although selenium was identified in several tissues, the levels were not reported.

Buchan (1974) cites a patient who was said to have developed nervousness, mental depression, metallic taste, vomiting, and pharynitis following the use of selenium red lipstick. Although selenium sulfide used in shampoo is relatively inert, a 46-year-old female using excessive amounts on abraded skin developed progressive generalized tremor, abdominal pain, metallic taste, and a garlic breath odor (Ransone, et al. 1961). These symptoms cleared when the use of the shampoo was discontinued.

Hadjimarkos proposed that an increase in dental caries is one of the toxic signs of excessive selenium intake, and showed that urinary selenium was twice as high in children with a high incidence of caries as in children with a low incidence (Hadjimarkos and Bonhorst, 1961; Hadjimarkos, 1969).

However, other studies have shown inconsistent (Muhleman and Konig, 1964) or marginally significant (Ludwig and Biddy, 1969) relationships between prevalence of dental caries and levels of selenium in the diet. It should be noted that an increased incidence of caries was produced in rats fed high levels of dietary selenium (Buttner, 1963).

Selenium may be inhaled as fumes or dust, or absorbed through the skin or gastrointestinal tract. Marked irritation of the nasal conjunctival, and tracheobronchial mucosa occurs rapidly, leading to cough, wheezing, dyspnea, chemical pneumonitis, and pulmonary edema. Low-grade fever may complicate the chemical pneumonitis. Abdominal pain, nausea, vomiting, and diarrhea ensue. Acute and chronic dermatitis of exposed or unexposed areas of the skin commonly occurs (Glover, 1970).

Hepatic necrosis has not been observed following exposure of man to selenium, but detailed analyses of liver function have not been performed. Myocarditis, known to occur in animals poisoned with inorganic selenates (Harr, et al. 1967), has not been reported in humans. Workers exposed to selenium have been noted to complain of nervousness, fatigue, depression, and pallor. A garlic odor of breath (and sweat) due to the pulmonary excretion of dimethyl selenide is one of the first signs of selenium absorption; a similar odor has been observed, however, after absorption of tellurium, because of dimethyl telluride excreted via the lungs. Metallic taste is commonly reported after selenium ingestion (Shapiro, 197[illegible]).

Nagai (1959) observed hypochromic anemia and leukopenia in Japanese women and children exposed to selenium in a rectifier manufacturing plant.

Studies have not shown changes in various blood constituents in man to be caused by acute or chronic selenium poisoning; however, selenate or selenite feeding has been found to increase serum cholesterol and aeotic lipids in the rat (Schroeder, 1968), while hypoglycemia has been produced in rabbits by the injection of selenite (Levine and Flaherty, 1926). Tsuzuki, et al. (1960) noted both decreased cholesterol levels and increased urinary protein in mice fed selenium.

Data from Westermarck, et al. (1977) show that no toxic manifestation was seen in nine Neuronal Ceroid Lipofuscinosis patients treated with 0.05mg Se/kg body weight daily for over one year. According to laboratory tests, there were no signs of impaired kidney, liver, or pancreas function during the treatment.

Synergism and/or Antagonism

Interrelationships of selenium toxicity with arsenic, mercury, cadmium, silver, and thallium have been described (Diplock, 1976).

Moxon (1938) established that the chronic and acute toxicity produced by the feeding of grains containing selenium at 15 μg/g could be alleviated or prevented by administration of arsenic at 5 mg/l as sodium arsenate in the drinking water. It was shown that either arsenate or arsenite was equally effective, and the selenium could be presented as seleniferous grain, selenite, or selenocystine (Moxon, et al. 1944, 1945, 1947; DuBois, et al. 1940; Thapar, et al. 1969; Ganther and Baumann, 1962). Ganther and Baumann (1962) used subacute dosages of arsenic and selenium and found that excretion of selenium into the gastrointestinal tract was stimulated by arsenic. Levander and Baumann (1966) demonstrated that selenium is excreted in the bile of arsenic-treated animals. The amount of selenium excreted into the bile of rats prepared with acute biliary fistulas increased by 10-fold during the first three hours following arsenic administration. When the arsenic to selenium dosage ratio was maintained at two, arsenic was shown to have an effect on biliary excretion of selenium when the dietary level of selenium was as low as 1.02 mg Se/kg. Levander (1972) suggested that arsenic protection against selenium toxicity may be mediated by combination of arsenic with selenium in the liver to form a conjugate that is readily excreted into the bile.

Kar, et al. (1960) found that the cadmium-induced lesions in the testes could be prevented by the administration of selenium. Mason and Young (1967) reported that the testicular injury produced by single subcutaneous injections of 0.45 mg of cadmium chloride in rats was protected against by half-equimolar selenium dioxide injected at the same time as cadmium. Protection was also provided by daily subcutaneous injections of half-equimolar selenium dioxide given over 6 successive days before cadmium was administered. Parizek, et al. (1968) and Gunn, et al. (1968) found that mortality rates of rats given otherwise lethal doses of cadmium was much reduced by the administration of selenium. Holmberg and Ferm (1969) found that the teratogenicity of cadmium was considerably reduced by selenium. Kar, et al. (1959) and Parizek, et al. (1968) found that selenium would prevent cadmium-induced damage to the nonovulating ovary in the rat. Parizek, et al. (1968) and Parizek (1964) found that administration of selenium could prevent necrosis and destruction of the placenta caused by exposure to small amounts of cadmium near the end of pregnancy. Similarly, cadmium-induced toxemia of pregnancy could be prevented by selenium (Parizek, 1965).

Levander and Argrett (1969) described the effect of mercury salts on the metabolism of selenium. Parizek and Ostadalova (1967) demonstrated that small amounts (0.02 mmole/kg) of sodium selenite (Na_2SeO_3), when given to rats intoxicated by a lethal dose (0.02 mmole/kg) of mercury ($HgCl_2$), completely protected the kidneys or intestine of these animals and ensured their survival. Further experiments revealed that the protective effect of selenite was not connected with an increased excretion of mercury, but on the contrary, with a marked decrease in mercury elimination through the urine (Parizek, et al. 1971). Levander and Argrett (1969) reported that mercury increased the retention of selenium in the blood, kidneys, and spleen. Parizek, et al. (1971) found that the transport of mercury across the placenta in pregnant rats was decreased by selenium, and less mercury was secreted into the milk. The bioavailability of selenium was much lower in the rats treated with mercury. Ganther, et al. (1972) showed that Japanese quail given 20 µg/g of mercury as methylmercury in diets containing 17 percent tuna survived considerably longer than quail given the same amount of methylmercury in a corn-soya diet. It was also found that when a number of different batches of tuna were analyzed for mercury and selenium, there was a striking correlation between the levels of selenium and mercury. Those batches that had little selenium contained little mercury (1.91 µg/g Se: 0.32 µg/g Hg), and when the mercury level was high the selenium level was also high (2.91 µg/g Se: 2.97 µg/g Hg). These results suggest that the higher selenium content of the tuna-supplemented diet acted to reduce the toxic effect of the additional methylmercury ingested by the quail.

In another experiment on synergistic effects with methylmercury, rats were fed a basal diet containing 20 percent casein with and without the addition of selenium at 0.5 µg/g as sodium selenite. It was found that mercury at 10 µg/g as methylmercury produced 100 percent mortality after six weeks of feeding, but selenium was completely effective in preventing mortality.

Diplock, (1976) and Grasso, et al. (1969) found the 0.15 percent of silver acetate in the drinking water produced toxicity symptoms in rats and chickens fed vitamin E-deficient diets; rats suffered from dystrophic lesions, necrotic degeneration of the liver, and high mortality and chickens suffered a pro-exudative effect. Supplementation with selenium (0.05 µg/g) had little effect, whereas the addition of 1 µg/g of selenium to the diet resulted in 55 percent protection against the toxic effects of silver. Grasso, et al. (1969) studied the lesions produced in the liver by silver and the lesions caused by dietary deprivation of vitamin E and selenium. The lesions were similar.

Hollo and Sztojcso (1960) demonstrated that death due to thallium poisoning could be prevented by the parenteral administration of selenate. Rusiecki and Brzezinski (1966) found that oral administration of selenate prevented the toxicity of thallium and that the content of thallium in liver, kidneys, and bones was increased by the selenate. Levander and Argrett (1969) showed that subcutaneous injection of thallium acetate increased the retention of selenium in liver and kidney and decreased the pulmonary and urinary excretion of selenium.

Halverson and Monty (1960) have demonstrated that dietary sulfate will partially restore selenium-poisoned rats receiving a purified diet with selenium added as selenite or selenate. Sulfate levels of 0.29, 0.58, and 0.87 percent as sodium or as potassium salts progressively relieved the growth inhibition due to selenium. Alleviations of greater than 40 percent were observed. Sulfate, however, did not substantially prevent liver degeneration due to selenium. In a later study, Halverson, et al. (1962) found that the addition of sodium sulfate to diets containing 10 µg/g of selenium was added as selenate, but did not when it was added as selenite or as wheat containing selenium. A similar but less pronounced effect was observed with sodium thiosulfate and sodium sulfite added to the seleniferous diets.

Levander and Morris (1970) used a peanut-meal diet and found that neither methionine nor vitamin E alone gave much protection against hepatic damage produced by excessive selenium. Combinations of methionine and vitamin E were effective, and the degree of protection was approximately proportional to the concentration of vitamin E added to the diet. Selenium concentrations of the liver and kidneys from rats fed the diets supplemented with methionine and vitamin E were less than those of the same organs from rats fed either methionine or vitamin E alone or no supplement.

Moxon and Dubois (1939) demonstrated that fluoride increases the toxicity of selenium in rats. They added 5 mg/l of fluoride to the drinking water of rats fed a diet containing selenium at 11 μg/g as seleniferous grain. Mortality was increased while weight gains and feed and water intake decreased. Hadjimarkos (1965, 1969) tested the interaction of selenium and fluoride by feeding both elements at levels 3 and 50 mg/l to one group of rats and only selenium at 3 mg/l to another group of rats. He did not observe an increase in the severity of signs of selenium toxicity in the group that received both fluoride and selenium.

Mutagenicity

Fishbein (1977) has recently reviewed the literature concerning the cytogenic and mutagenic effects of selenium. Selenium has been shown to affect the genetic process in barley (Walker and Ting, 1967) and in *Drosophila melanogaster* (Ting and Walker, 1969; Walker and Bradley, 1969). Treatment with sodium selenite before meiosis caused structural alterations in the meiotic chromatin and decreased the genetic recombination in barley (Walker and Ting, 1967). Genetic crossing-over in *D. melanogaster* was reduced by selenoamino acids. For example, selenocystine at 2 μM had a significant effect on crossing-over in the X-chromosome of *D. melanogaster*

(Ting and Walker, 1969; Walker and Bradley, 1969). They found that urethane and selenocystine interacted antagonistically at certain levels and synergistically at other levels.

Sentein (1967) found that selenates and selenites have an effect on segmentation mitoses similar to that of SeO_2; polar dissociation with conserved dominance of the principal pole, stickiness, and clumping of chromosomes. Fokina and Kudryavtseva (1969) found that sodium selenite solution caused cell degenerative changes and decreased the mitotic activity when added in unspecified dilutions to rabbit kidney tissue cultures.

Paton and Allison (1972) have reported the effects of sodium selenate and sodium selenite on chromosomes in cultures of human leukocytes and diploid fibroblasts. Subtoxic doses of sodium selenate and sodium selenite were added to leukocyte cultures and fibroblast cells at various times between two and 24 hours before fixation. No chromosome aberrations were observed for either selenium salt; cells were exposed to at least two concentrations of each selenium salt for 24, 48, or 72 hours.

Craddock (1972) reported that selenomethionine acts as a methyl donor in the methylation of DNA, transfer RNA, and ribosomal RNA in the intact rat. The relative amounts of the different methylated bases formed in each nucleic acid were similar to those found after injection of (^{14}C) methylmethionine. He has suggested that it is likely that selenoadenosyl selenomethionine (Se-A SeM), which is known to be formed from selenomethionine *in vivo*, is a methyl donor in no way different from S-adenosylmethionine in the reactions catalyzed by the nucleic acid methylating enzymes.

Teratogenicity

The National Academy of Sciences (1976) has thoroughly summarized and reviewed the literature concerning the teratogenic effects of exposure to selenium compounds. Hence, the material in this section is quoted from that review.

> The embryo of the chick is extremely sensitive to selenium toxicity. Hatchability of eggs is reduced by concentrations of selenium in feeds that are too low to produce symptoms of poisoning in other farm animals. Poor hatchability of eggs on farms has therefore proved to be an aid in locating potentially seleniferous areas where alkali disease in cattle, hogs, and horses may occur (Rosenfeld and Beath, 1964). The eggs are fertile, but some produce grossly deformed embryos, characterized by missing eyes and beaks and distorted wings and feet (Carlson, et al. 1951; Franke, et al. 1936; Franke and Tully, 1935; Gruenwald 1958). Inherited abnormalities, such as the creeper mutation in hens, exaggerated the developmental malformations caused by selenium (Landauer, 1940). Deformed embryos were also produced by injection of selenite into the air cell of normal, fertile eggs of both hens (Franke, et al. 1936) and turkeys (Carlson, et al. 1951). Kury, et al. (1967) suggested that if the definition of teratogenic effects is expanded to include more than dead or grossly abnormal embryos, the adverse effects of raising chickens on seleniferous soils could be more widespread than has been realized. This conclusion is based on their findings of anemia (low red-blood-cell counts and hemoglobin values) in normal as well as malformed embryos of chicks following injections of seleneous acid into fertilized hen's eggs.
>
> The consumption of seleniferous diets interfered with the normal development of the embryo in many mammalian species, including rats (Franke and Potter, 1935; Rosenfeld and Beath, 1964), pigs (Wahlstrom and Olson, 1958), sheep (Rosenfeld and Beath, 1964), and cattle (Dinkel, et al. 1963). In sheep, malformations of the eyes and of the joints of the extremities have been reported. The latter cause deformed legs and impaired locomotion (Rosenfeld and Beath, 1964). These malformations were also observed in chicks. Holmberg and Ferm (1969), however, did not observe teratogenic or embryotoxic effects in hamsters after intravenous administration of near lethal doses of sodium selenite.
>
> Robertson (1970) suggested that selenium may be a teratogen in man. Reports in the older literature of the people in Colombia eating toxic grains referred to malformed babies born to Indian women (Rosenfeld and Beath, 1964). Robertson gathered information on the possible association between abnormal pregnancies and the exposure of women to selenite. Out of one possible pregnancy and four certain pregnancies among women exposed to selenite, only one pregnancy went to term, and the infant showed bilateral clubfoot.

> Of the other pregnancies, two could have been terminated because of other clinical factors. Shamberger (1971) cautions against using the inverse relationship between neonatal deaths and the level of selenium in some parts of the United States as a basis for a conclusion concerning the role of selenium in teratogenicity in human beings. Because of the many other factors in our environment that could influence the biological availability of selenium, it appears that we would be unjustified in concluding, solely on the basis of this evidence, that selenium has no bearing on teratogenicity in human beings. Rosenfeld and Beath (1964) emphasized that studies of mammalian malformations in relation to the age of the embryo or fetus and its susceptibility to selenium would be of great value to basic as well as applied research.

Carcinogenicity

Since the 1940's, numerous research studies have demonstrated the toxicity of organic and inorganic selenium compounds to humans and domestic and laboratory animals. Most of the toxicologic projects have investigated the effects of acute and chronic exposures over periods of time significantly less than a lifetime. These studies have failed to demonstrate a significant increase in malignant tumor rates among the selenium-exposed animals versus controls not exposed to selenium. Only six long term toxicologic research projects provide information concerning the carcinogenic potential of selenium compounds. The studies can be summarized as follows:

Nelson, et al. (1943): The study was designed to determine the lower level of selenium necessary to produce chronic toxicity. Seven groups of 18 female rats each (inbred Osborne Mendel strain) were fed selenium in organic combination with corn and wheat or in a mixed inorganic selenide solution (a solution of ammonium potassium sulfide and ammonium potassium selenide, containing 48 gm of Se per liter of solution). Beginning at three weeks of age, rats received Se of 5, 7, and 10 μg/g of diet. Mortality was high and found to be approximately proportional to the level of dietary selenium (Table 6). One hundred twenty-six rats were divided into seven groups of 18. Only 53 survived 18 months; 39 survived 24 months. Of the 53 rats that

TABLE 6

Death and Survival Information*

Level of Selenium	Number of Deaths by Time Period Months				Number of Survivors at End 24 Months	Number of Rats in Each Group at Start of Experiment
	3-	3 1/2-11 1/2	12-17 1/2	18-23 1/2		
5 µg/g (corn)	2	1	5	1	9	18
5 µg/g (wheat)	0	1	3	4	10	18
7 µg/g (corn)	7	0	1	3	7	18
7 µg/g (wheat)	9	2	3	1	3	18
10 µg/g (corn)	13	0	0	2	3	18
10 µg/g (wheat)	12	1	2	2	1	18
10 µg/g (selenide)	2	6	3	1	6	18
Total Experimental	45	11	17	14	39	126
Control	0	2	2	2	12	18

*Source: Nelson, et al. 1943

survived 18 months, 11 developed liver tumors diagnosed as hepatic cell adenomas or low grade hepatic cell carcinomas, and four others had pronounced adenomatoid hepatic cell hyperplasia that could be interpreted as a transition to tumor. In the 73 rats that died, or were sacrificed before 18 months, there were no tumors and no advanced adenomatoid hyperplasia, although cirrhosis was fairly frequent (after three months). The 14 control rats that lived at least 18 months had neither adenomatous and neoplastic lesions nor cirrhosis. The spontaneous incidence of hepatic tumors in the colony (source of control animals) at that time was 0 percent in rats less than 18 months old, 0.5 percent in rats 18 to 24 months old, and 0.9 percent in rats finishing a 2-year experimental or control period. None of the tumors in the test animals had metastasized. No tumors occurred in livers that were not cirrhotic. Nelson, et al. (1943) provided this description of the livers and tumors:

> Upon microscopic examination, portions of the peripheries of the tumors were found separated from the rest of the liver by collagenous fibers, but there was no complete encapsulation. The growths were composed of fairly regular to irregular cords of hepatic cells, usually more oxyphilic than the surrounding liver in the adenomas and less oxyphilic in the carcinomas. Some tumors showed no mitoses after several minutes search and in others a few or even a moderate number were seen in a shorter time. Bile duct proliferation was slight except in one instance where the peripheral 1 to 2 mm of a 3-cm tumor was composed of small bile ducts. Hemosiderin pigmentation and fibrosis within the tumors were not striking; focal necrosis was seen rarely, and hemorrhage not at all. Fatty degeneration was slight and was the same as, or a little less than, in the surrounding liver; the livers of the selenium control rats also showed a slight fatty degeneration which was not found in our other control groups on more adequate diets. A few of the tumors enclosed small foci of myeloid cells, and in a few there were small cystic areas. Since sections were not made of every tumor, some livers listed as showing adenoma may have also contained carcinoma and vice versa.
>
> The differentiation between adenoma and low-grade carcinoma was difficult to make in this series of tumors; the latter showed greater irregularity of liver cell cords, decreased oxyphilia of liver cells, more mitotic figures, and an invasive tendency at their margins.

Harr, et al. (1967); Tinsley, et al. (1967): The National Cancer Institute funded a contract with Oregon State University to further investigate the toxicity and carcinogenicity of selenium ions. A total of 1,437 Wistar rats from the University-maintained colony were assigned to 34 different dietary groups. Selenium levels ranged from 0.5 to 16 µg/g (as dietary sodium selenite and sodium selenate) in animals maintained on high and low protein basal rations (22 percent casein, 12 percent casein, and 12 percent casein plus 0.3 percent DL- methionine). Both male and female rats were included in the experiment but the number of each assigned to the individual dietary groups was not reported. The age of the animals at the time of initial exposure was also not reported, but, with the exception of 136 animals that were killed at specific ages, all animals were maintained until death or until moribund, at which time they were sacrificed. Since the primary purpose of the study was to evaluate the carcinogenic potential of selenium, a suspect hepatocarcinogen, N-2-fluorenyl-acetamide (FAA) was fed at dietary levels of 100 and 50 µg/g to establish the index of carcinogenesis in the colony. Nine of the dietary groups with a total of 335 animals were used in complementary experiments to test such things as exposure to multiple dose levels, intermittent exposures, and limited feed intake.

Due to excessive losses in the high selenium groups (16 µg/g selenite + 22 percent casein, 16 µg/g selenate + 22 percent casein, and 8 µg/g selenate + 12 percent casein), the animals in these groups were sacrificed early. One hundred seventy-five rats lived 2 years or more (Table 7). The rats on the control diets showed no evidence of malnutrition. The hepatic changes of the older animals included accentuated lobular pattern, hyperemia, cellular degeneration, mildly proliferative hepatocytes, double nuclei, and multiple nuclei.

TABLE 7

Rats Living 2 Years[a]

Dietary Selenium Level (μg/g)	Oxidation State	Casein (percent)	Total Number on Diet	Number Living 2 Years
0	-	22	110	24
0.5	selenite	22	55	17
2.0	selenite	22	54	14
0.5	selenate	22	56	11
2.0	selenate	22	55	11
0	-	12	109	29
0.5	selenate	12	55	12
2.0	selenate	12	54	6
0	-	12[b]		
			34	10
4	selenate	12	53	1
Commercial Diet	-		55	13
8 (fed alternate weeks)	selenate	22	40	14
4 (fed alternate weeks)	selenate	12	40	13
		Totals	770	175

---

[a] Source: Harr, et al. 1967

[b] Added 0.3 percent DL-methionine

Eleven hundred twenty-six out of the original 1,437 animals were autopsied. Acute toxic hepatitis was generally observed in animals receiving selenium added to the semipurified diets at the rate of 4, 6, 8, or 16 µg/g and in the commercial diet with 16 µg/g of added selenium. The typical animal lived less than 100 days. The surface of the liver was mottled with pale yellow or white areas and the margins of the lobes were stippled with pale foci. Parenchymatous degeneration was present. The cytoplasm of the hepatic cells was finely granular and eosinophilic. Some of the animals suffered from chronic toxic hepatitis. There were three gross variations in the affected livers: (1) small hobnailed surface, (2) irregular mottled surface, and (3) diffusely enlarged liver. Hyperplastic lesions predominated in the livers of about 50 percent of the selenium-fed animals which lived more than 282 days.

Sixty-three neoplasms were found in the study (Table 8). Forty-three occurred in the 88 rats fed FAA. The other 20 were randomly distributed through the experimental diets and included no hepatic neoplasms.

Thus, although lifetime exposures to toxic levels of selenium were found by these workers to produce drastic changes in liver and other organs of rats, no hepatic cancers were observed among the selenium-exposed animals. The total number of cancers and the site distribution appear similar to that observed in the controls.

Harr, et al. (1967) concluded that neoplasia in the rat are not induced by selenite, selenate, or by methionine and selenate.

Scott (1973) has provided some discussion concerning the potential causes for the differences in results observed by Nelson, et al. (1943) and

TABLE 8

Distribution of Neoplasms in Experimental Diets*

Diet			Neoplasms				
Type	Selenium (µg/g)	No. Necropsies	No.	Type	Age		
					Low	Med	High
Selenite with 22 percent casein	0.5	49	1	Uterine polyp	-	752	-
			11	lipoma	-	450	-
	2.0	47	1	Mammary cancer	-	174	-
	6.0, 8.0, 16.0	65	-	-	-	-	-
Selenate with 22 percent casein	0.5	44	1	Uterine cancer	-	380	-
	2.0	41	1	Lymphoma	-	563	-
			1	Fibroma	-	500	-
	8.0	37	1	Urinary cancer	-	43	-
	4.0, 6.0, 16.0	54	-	-	-	-	-
Selenate with 12 percent casein	0.5	47	1	Mammary cancer	-	722	-
			1	Lymphoma	-	730	-
	2.0, 4.0, 6.0, 8.0	103	-	-	-	-	-
Selenate with methionine	4.0	38	-	-	-	-	-
	6.0	13	-	-	-	-	-
	8.0	15	-	-	-	-	-
FAA 100 µg/g 22-percent casein	0	45	12	Hepatic cancer	243	313	512
			7	Mammary cancer	243	308	578
			3	Lymphoma	154	247	282

TABLE 8 (cont.)

Diet		Neoplasms					
Type	Selenium (µg/g)	No. Necropsies	No.	Type	Age Low	Age Med	Age High
Controls: 12 percent casein	0	98	3	Mammary cancer	92	548	707
			1	Lymphoma	-	356	-
			1	Lipoma	-	731	-
22 percent casein	0	103	3	Mammary cancer	620	678	731
			1	Fibroma	-	458	-
12 percent casein + 0.3 percent DL-methionine		29	1	Broncho cancer	-	434	-
Commercial diet		46	1	Lymphoma	-	578	-
Variable Selenium and control diets		206	-	-	-	-	-

*Source: Harr, et al. 1967

Harr, et al. (1967). Some of the possible (based on the available information, it is impossible to conclusively determine the causes for the differences) explanations are:

1. Nelson and associates used the Osborne Mendel strain of rats whereas Harr and associates used the Wistar strain. It is possible that the two strains may have genetic differences that affect the biologic response to selenium.

2. Harr and associates fed sodium selenate or sodium selenite to provide the levels of dietary selenium, whereas the Nelson group used various levels of seleniferous corn and wheat to provide the selenium levels in most of their work. Nelson, et al. (1943) report tumors in two rats which had received 10 µg/g of selenium in a mixture of ammonium potassium sulfide and ammonium potassium selenide. Nelson, et al. (1943) did not feed a control group ammonium potassium sulfide alone, nor did they have a spectrophotometric analysis of the seleniferous grains to determine whether or not these grains may have been contaminated with a known carcinogen.

3. Nelson, et al. (1943) reported hepatomas only in rats that also showed cirrhosis.

4. The hyperplasia and "hobnail" appearance of the livers which Harr and associates observed may have been much more severe in rats already suffering from cirrhosis, thereby forming foci which resembled tumors.

Cherkes, et al. (1962); Volgarev and Tscherkes (1967): In three series of experiments, selenium was fed as sodium selenate to 200 heterozygous rats at the rate of 4.3 or 8.6 µg/g of feed. The feeds were not semipurified.

[redacted]

They contained 12 to 30 percent protein with addition of riboflavin, methionine, atocopherol, cystine, nicotinic acid, and choline in appropriate groups. In the third series, a set of 200 control rats were fed a stock diet and observed for a longer period of time than the experiment.

In the first series, 40 rats were fed 4.3 μg/g of selenium as sodium selenate plus 12 percent casein in the diet. No indication was given as to the age or weight of the animals at the start of the experiment, but it is assumed weanling rats were used. In the 23 rats surviving 18 months or longer, 10 developed tumors, and 4 had precancerous lesions; no information is given concerning the 17 rats that died prior to 18 months. Of the 10 rats with tumors, 4 developed sarcomas, 3 developed hepatic carcinoma (2 with metastases to the lungs), and 3 had hepatocellular adenomas. Of the 13 noncancerous rats, 4 had lesions termed precancerous. The lesions were cholangiofibrosis, oval cell (bile duct cell) proliferations, and biliary cysts. There was no indication as to when the tumors appeared other than the statement that they were seen some time after the 18th month. No control rats were included in this series.

In the second series, 60 male rats, divided into three groups of 20, were fed 4.3 μg/g of selenium in a 12 percent casein diet for six months and then subjected to liver biopsy. Group I was maintained on 12 percent casein but the level of selenium was increased to 8.6 μg/g of diet commencing with the seventh month. Group II was fed 8.6 μg/g of selenium in the diet but the casein level of the diet was raised to 30 percent. Group III received the same diet as Group II with the addition of riboflavin. Protein levels in Groups II and III were increased to 30 percent to prevent possible death losses from the increased selenium levels.

The biopsy specimens collected at the end of 6 months showed mild degenerative changes in the liver but no lesions that could be classified as cancerous or precancerous.

The 18 surviving rats in Group I at the end of 6 months died within the next 6 months following the increase of selenium to 8.6 µg/g of the diet. Microscopic examinations revealed characteristic histologic changes of selenium intoxication. There were no cancerous or precancerous changes in the liver.

Seventeen of the original 20 rats assigned to Group II were surviving at the end of the initial 6-month period. Increasing the dietary selenium level from 4.3 µg/g to 8.6 µg/g while also increasing the protein level to 30 percent appeared to have no effect on survival since 16 animals still remained at the end of one year and 12 lived more than two years. At 14 months, sarcomas were found in two rats, one of the mediastinum, the other of the mesenteric lymph nodes. A third rat had liver cirrhosis with multiple nodules. No precancerous lesions similar to those in series one were found. The rats examined after one year of exposure showed changes characteristic of chronic selenium poisoning. Degenerative and atrophic changes in the liver and spleen were observed in rats surviving two years.

Seventeen of the 20 rats assigned to Group III died within the first year. Of the three rats surviving over one year, one developed a sarcoma of the mesenteric lymph nodes that was found at 19 months, another had hyperplasia of the liver cells with some nodules of hepatocellular adenoma, and the third rat had only degenerative changes in visceral organs.

In the third series, 100 heterozygous male rats weighing 100 gm each were allocated into five groups of 20 animals each and placed on a basal diet containing 12 percent casein and 4.3 µg/g of sodium selenate.

Additives were included in the group diets in order to test their effects on the development of possible selenium-induced carcinogenesis. The assignment of dietary additives was as follows:

Group I : no additives

Group II : methionine at 5,000 µg/g and a-tocopherol at 10,000 µg/g

Group III: cystine at 5,000 µg/g

Group IV : nicotinic acid at 5 mg per rat per day

Group V : choline at 35 mg per rat per day

All of the rats in Group I were dead by the 26th month, 10 months shorter than similarly fed animals in series one. The animals in Groups II, IV, and V were sacrificed at the end of the 25th, month and those in Group III at the end of the 17th month. None of the animals possessed tumors or precancerous lesions. No spontaneous tumors were observed in the 200 heterozygous male control rats fed stock ration.

Volgarev and Tscherkes (1967) have suggested that the reason for the difference in tumor rates between the series one and series three may be explained by the fact that the experiments of series three were started 2 years later than series one and involved animals obtained from a different source. They note, however, that of 10,000 other rats used in their laboratory, not a single case of spontaneous liver cancer was seen. No information is provided concerning the examination methods, exposures, rat strain, etc. for the 10,000 rats.

According to Van Houwelling (1973), it has been discovered that the rats used in the first two series were infected with a parasite which is known to induce tumors; the specific parasite was not named. Hence, the results of this experiment are difficult to interpret.

Schroeder (1967); Schroeder and Mitchener (1971, 1972): Four hundred eighteen weanling rats of the Long-Evans strain [BLU: (LE)] born from random-bred females (purchased from Blue Spruce Farms, Altamont, N.Y.) were fed a diet of whole rye flour (60 percent), dry skim milk (30 percent), corn oil (9 percent), and iodized sodium chloride (1 percent), to which were added vitamins and iron. The rats were divided into 4 groups of approximately 100 animals each. One group served as a control, and the second, third, and fourth groups received 2 to 3 mg/l of sodium selenate, sodium selenate, and 2 mg/l of tellurite in the drinking water. Within a group, the results are reported separately by sex. Because selenite was very toxic to male rats, causing 50 percent mortality in 58 days, sodium selenate was substituted at 2 mg/l until one year of age when the level was raised to 3 mg/l. There were no significant differences in the weights of male rats fed selenate and their controls at any interval up to 36 months old. Since selenite was not as toxic for females (50 percent mortality at 348 days), sodium selenate was not substituted for selenite and the dose level continued at 2 mg/l.

The diet contained approximately 24 percent protein, 65 percent carbohydrate, and 11 percent fat on a dry basis, at 396 kcal/100 g. Selenium content of the diet was 0.05 μg/g, wet weight.

When the rats were 21 months old, an epidemic of virulent pneumonia struck the colony with considerable loss of life. It was controlled with penicillin in drinking water in about three weeks. Losses in the various groups were as follows (percent): male controls 36.5, selenate 48.9; female controls 27.2, selenate 14.8.

The average weights of male and female groups of selenium-supplemented rats were 3 to 7 percent greater than the corresponding nonsupplemented control groups for each 6-month age period after one year of age, except for males at 18 months (controls were 1.7 percent heavier).

Approximately 75 percent of the control and selenate animals living prior to the epidemic of pneumonia at 28 months were autopsied. Histological examinations were performed on 65 control and 48 of the selenate exposed rats. The criteria used to select animals for autopsy or histologic examination was not reported. Ages of animals at autopsy are not provided.

Eleven malignant tumors were found in the control animals and 20 were reported in the selenate-supplemented animals. The types of tumors and the numbers were given as follows:

Tumor Type	Control Group	Selenate Group
Mammary	5	3
Spindle cell sarcoma	2	4
Leukemia types	2	4
Pleomorphic carcinoma	1	2
Leiomyosarcoma	1	
Malignant hamartomas		2
Undifferentiated sarcoma		1
Round cell sarcoma		1
Malignant glioma		1
Ovarian adenocarcinoma		1
Spindle cell sarcoma invading the heart		1
	11	20

The anatomical locations of the sarcomas and pleomorphic carcinomas were not reported. These tumors may have been sclerosed granulomas secondary to the epidemic of pneumonia. Histologic slides were prepared only from selected organs and animals, and the rationale for that selection was not reported. Since the organs and tissues were not systematically searched, type and incidence of histologic lesions are not known (NAS, 1976). No information concerning types and numbers of tumors by sex within groups is reported.

Malignant tumors in the selenite-fed rats included a reticulum cell sarcoma, and three spindle cell sarcomas invading the heart.

Very little malignant tumor information is given concerning the male and female groups initially fed selenite. Due to the toxicity of selenite the exposure for males was changed to selenate and both groups were sacrificed prior to the age of high tumor incidence.

Schroeder and Mitchener (1972) repeated the rat studies in mice. Here, treatment with 3 mg/l of selenium via the drinking water did not have a significant effect on the incidence of spontaneous tumors.

National Cancer Institute (1978): During June 1978, the U.S. Environmental Protection Agency received a copy of the data sheets for a National Cancer Institute-supported bioassay study of selenium disulfide conducted at Hazleton Laboratories. No formal write-up with project description, interpretation, or conclusions was received.

Eight groups (four female and four male) of mice (stock/strain $B6C3F_1$) were included in the lifetime bioassay study; each group contained 50 animals. The four groups for each sex were defined as follows: untreated control (animals kept in the same environment and fed a similar diet to treated animals but did not receive anything by gavage); vehicle control (animals kept in same environment and fed a similar diet to treated animals but received the vehicle-carboxymethyl cellulose, by gavage); low dose test (20 mg/kg of selenium disulfide, or 11.05 mg/kg of selenium); and high dose test (100 mg/kg of selenium disulfide, or 55.24 mg/kg of selenium). Oral administration was initiated about two months after birth and continued once daily for the remainder of life (up to 728 days).

From the raw data sheets it is apparent that the strain of mice used had a high rate of spontaneous tumors of multiple anatomic sites (Table 9). For male mice, the malignant tumor incidence for the selenium disulfide

TABLE 9

Tumor Incidence for Rats Exposed to Selenium Disulfide*

Anatomic Site	Untreated Controls		Vehicle Controls		Low Dose (11.05 mg/kg)		High Dose (55.24 mg/kg)	
	Males	Females	Males	Females	Males	Females	Males	Females
Integumentary System	7^a(49)^b	1(50)	5(50)	1(49)	8(50)	1(50)	1(50)	1(49)
Respiratory System (Lung)	(49)	(50)	(50)	(49)	(50)	(50)	(50)	(49)
Adenocarcinoma, Nos, Metastic	0	0	0	0	1	0	0	1
Alveolar/Bronchiolar Adenoma	8	2	3	0	8	2	11	8
Alveolar/Bronchiolar Carcinoma	1	0	1	0	2	1	2	4
Other	3	0	5	0	3	0	3	0
Hematopoietic System								
Multiple Organs	6(49)	17(50)	4(50)	17(50)	12(50)	23(50)	8(50)	17(50)
Spleen	0(49)	0(50)	2(50)	0(49)	1(50)	1(50)	1(50)	3(49)
Mesenteric L. Node	0(49)	1(48)	0(50)	0(48)	0(49)	0(50)	1(50)	1(48)
Other	1(49)	-	1(22)	-	1(19)	-	0(19-50)	-
Digestive System								
Salivary Gland								
Adenocarcinoma, Nos	none	0(50)	none	0(46)	none	0(50)	none	1(49)
Liver	(49)	(50)	(50)	(49)	(50)	(50)	(50)	(49)

TABLE 9 (cont.)

Anatomic Site	Untreated Controls		Vehicle Controls		Low Dose (11.05 mg/kg)		High Dose (55.24 mg/kg)	
	Males	Females	Males	Females	Males	Females	Males	Females
Hepatocellular Adenoma	2	1	0	0	3	1	0	6
Hepatocellular Carcinoma	17	2	15	0	11	1	23	21
Hemangiosarcoma	0	0	2	0	1	1	1	0
Other	0	0	0	0	1	0	1	0
Pancreas	0(49)	1(50)	1(50)	0(49)	1(50)	0(50)	0(50)	0(49)
Stomach	1(49)	1(50)	1(49)	0(49)	0(49)	1(50)	0(48)	0(49)
Other	0(49)	1(50)	1(49)	0(49)	0(49)	1(50)	0(48)	0(49)
Urinary System	0(49)	none	1(50)	none	0(49)	none	1(50)	none
Circulatory System	0(49)	none	1(50)	none	0(50)	none	0(50)	none
Endocrine System	0(47-48)	2(45-50)	4(49)	3(42-48)	0(49)	2(37-50)	1(48-49)c	2(38-49)
Reproductive System	0(49)	4(50)	1(50)	8(49)	0(48)	6(50)	0(49)	5(49)
Nervous System	none	none	none	none	none	none	none	none
Special Sense Organs	0(49)	0(50)	2(50)	2(49)	1(50)	0(50)	0(50)	4(49)
Musculoskeletal System	none	0(50)	2(50)	2(49)	none	1(50)	none	0(49)
Body Cavities	none	none	none	none	none	none	none	none
All Other Systems	0(49)	none	2(50)	none	0(50)	none	0(50)	none

TABLE 9 (cont.)

Anatomic Site	Untreated Controls		Vehicle Controls		Low Dose (11.05 mg/kg)		High Dose (55.24 mg/kg)	
	Males	Females	Males	Females	Males	Females	Males	Females
Tumor Summary:								
Tot. Animals with Primary Tumors	31	26	29	24	35	31	36	42
Tot. Animals with Benign Tumors	11	7	8	7	13	10	14	15
Tot. Animals with Malignant Tumors	26	22	25	20	27	26	28	38
Tot. Animals with Secondary Tumors	3	1	7	0	3	0	2	1
Tot. Animals with Tumors Uncertain Benign or Malignant	0	0	0	0	0	0	0	2

*Source: National Cancer Institute, 1978

[a] number of tumors for a site or of a particular type for the site.

[b] number of animals examined for the specified anatomic site.

[c] number of animals examined for each tumor type for each site within the system varies between the specified range.

exposed groups was not significantly different from the control groups (Table 9); no significant differences were observed for specific anatomic sites or for the animals as a whole. However, the high dose female group had significantly more animals with hepatocellular carcinoma (21 out of 49 animals, or 43 percent) than the two control groups (2 out of 50, or 4 percent for untreated controls, and 0 out of 49 for vehicle controls). No other significant differences were observed for the females.

This experiment suggests that, at least in female mice, selenium disulfide is a carcinogen. Since selenium disulfide is not just another salt of selenium, but instead a separate and distinct compound, it cannot be assumed that these results show that inorganic selenium (selenite or selenate) compounds are carcinogenic. Clearly, similar bioassays are needed for inorganic selenium compounds.

From the studies just cited, it is apparent that the question concerning carcinogenicity of inorganic selenium has not been answered and will not be until several specifically designed lifetime bioassay studies are performed. Sufficient research has been completed to raise the possibility that inorganic selenium is a carcinogen, but none of the present studies produces a weight of evidence or conclusive dose response data for risk estimation. The Commissioner of the Food and Drug Administration has concluded that: (1) the available information does not support classification of selenium or its compounds as having carcinogenic activity, (2) the use of selenium as set forth by the Food and Drug Administration regulations constitutes no carcinogenic risks (38 FR 81 8229). The conclusions of the National Academy of Sciences (1976) report on selenium are:

> Despite an initial report of selenium as a carcinogen (Nelson, et al. 1943), chronic experimental exposure of rats and mice to selenium salts over a period of 12 years has not induced neoplasia (Cherkes, et al. 1962; Harr, et al. 1967; Nelson, et al.

> 1943; Schroeder, 1967; Schroeder and Mitchener, 1971, 1972; Shamberger and Frost, 1969; Tinsley, et al. 1967; Volgarev and Tscherkes, 1967). During the same period, selenium salts have been used propylactically and therapeutically in ruminants, omnivores, and carnivores throughout the world. Epidemiologic and demographic evidence from the widespread use of selenium supplementation, exposure to toxic concentrations of selenium in feeds, and use of selenium in shampoos and industrial plants, does not suggest that selenium is carcinogenic; rather, it may be correlated with a reduction in the evidence of human ovarian cancer (Frost, 1971; Schroeder and Mitchener, 1972; Anonymous, 1970; Shamberger and Rudolph, 1966; Shamberger, et al. 1972, 1973; Shamberger and Willis, 1971; Wedderburn, 1972).

The conclusion of the International Agency for Research on Cancer (IARC) is that the available animal data are insufficient to allow an evaluation of the carcinogenicity of selenium compounds. The available human data provide no suggestion that selenium is carcinogenic in man, and the evidence for a negative correlation between regional cancer death rates and selenium is not convincing (IARC, 1975).

It seems that the U.S. EPA must also conclude that there are not adequate data to determine if selenium compounds are carcinogenic.

Anticarcinogenesis: The National Academy of Sciences (1976) has thoroughly summarized and reviewed the literature concerning the anticarcinogenic effects of exposure to selenium compounds. Hence, the material in this section is quoted from that review.

> The demonstration of the relationship of selenium to human cancer is limited to demographic studies and comparisons of blood levels of selenium in patients with and without malignancies. However, Weisberger and Suhrland (1956) discussed the effect of selenium cystine on leukemia, and Chu and Davidson (1972) listed selenium compounds among potential antitumor agents.
>
> Demographic and experimental observations of Shamberger and associates support the concept of pharmacologic and medical uses of selenium salts (Schrauzer and Rhead, 1971; Shamberger and Frost, 1969; Shamberger, et al. 1973; Shamberger and Willis, 1971). They found an inverse correlation between the incidence of cancer deaths, the concentration of selenium in the patients serum, and geographic incidence of selenium -- low, moderate, or

high. The concentration of selenium in the blood of cancer patients averaged 74 percent of normal. However, the blood of patients with some forms of cancer contained normal concentrations of selenium.

The selenium contents of diets of 17 paired human males with and without gastric cancer were compared and related to dietary antioxidants and food preservatives (Shamberger, et al. 1972). Patients with gastrointestinal cancer or metastases to gastrointestinal organs had significantly lower levels of selenium in the blood than normal patients (Shamberger, et al. 1972). No elevations of selenium in the blood of cancer patients were noted. The authors postulated that selenium acted to prevent attachment of the carcinogen to DNA sites.

Solymosi (1963) also reported on the effect of adding sodium selenide to cancer-inducing preparations of anthracene compounds or adding sodium selenite to the feed of rats exposed to anthracene compounds. Rats fed dietary selenite, and those treated with preparations of anthracene compounds with added selenide, developed fewer skin papillomas than rats treated with anthracene compounds without added selenide.

Harr, et al. (1972) reported that after 200 days of feeding selenium-depleted rats a semipurified feed containing 100 ng of the hepatic carcinogen FAA per gram of feed and 0.1, 0.5, or 2.5 µg of added selenium as selenite per gram, the incidence of mammary and hepatic neoplasia (with or without 0.1 µg of added selenium per gram) was three times greater than the incidence in rats supplemented with 0.5 or 2.5 µg of selenium per gram. The low-selenium groups (0 and 0.1 µg/g) died before 200 days of age and had a 90 percent incidence of neoplasia. At this time, 35 percent of the rats fed 0.5 and 2.5 µg of selenium per gram had died, and the incidence of neoplasma was 30 percent. Most of the remaining rats fed 0.5 and 2.5 µg of selenium per gram lived for an additional 120 days. By this time, they had received the carcinogen for an additional 120 days, and the total incidence of neoplasma was 90 percent, as observed in the groups receiving 0 and 0.1 µg of selenium per gram. Since the longevity of the rats was proportional to the amount of selenium supplementation and the duration of exposure to the carcinogen, the increase in cancer in the rats, heavily supplemented with selenium, may have been due to greater exposure to the carcinogen or to longer time for induction.

The mammary tumors in the group not supplemented with selenium were more invasive than those in rats from the three supplemented groups and predominated in the pelvic rather than in the thoracic region, as in the selenium-supplemented or commercially fed rats.

Johnston (1974) studied the effect of selenium on the induction of cancer by FAA and diethylnitrosamine in selenium-depleted rats over a restricted exposure period. Because of widely varying rates of feed consumption by the principal and control groups and the high incidence of neoplasia in all the exposed groups, results were confusing.

Jacobs, et al. (1977) studied the effect of sodium selenite at 4 mg/l in drinking water on the incidence of colon cancers in rats induced by DMH (1,2 dimethylhydrazine) or MAM (methylazoxymethanol acetate). Rats receiving DMH and no selenium exhibited 87 percent tumor incidence (13 of 15 rats had tumors). Selenium significantly ($p=0.025$) decreased the incidence of colon tumors induced by DMH such that only 6 out of 15 rats had no tumors. No significant difference in tumor incidence was apparent between groups receiving MAM with or without selenium supplements.

The unique ability of selenium to reduce methylene blue was reported by Schrauzer and Rhead (1971), who suggested that this ability might provide a basis for testing for cancer or susceptibility thereto. Clayton and Baumann (1949) have reported on the relation between diet and azo dye tumors. In studies of lipid therapy, based on the types of lipid imbalance in cancer patients, Revici (1955) reported that the most satisfactory and reproducible palliative effects were obtained by using synthetic lipids containing bivalent selenium, a serendipitously acquired observation alluded to by Frost (1971). Berenshtein and Aleshko (1968) have described the effect of selenium on lipid metabolism.

Nutritional Essentiality of Selenium and Its Role in Human Nutrition

Schwarz and Foltz (1957) first reported a beneficial nutritional effect of selenium when they observed that trace levels in the diet protected vitamin E-deficient rats against necrotic liver degeneration. Soon thereafter, selenium was shown to protect against a variety of vitamin E-associated animal diseases such as exudative diathesis in chicks and white muscle disease in lambs and calves (Schwarz, 1961). In 1968, nutritional deficiencies of selenium per se were demonstrated in chicks (Thompson and Scott, 1969) and rats (McCoy and Weswig, 1969) fed adequate levels of vitamin E. Signs of deficiency specific for selenium in these species include pancreatic degeneration in chicks (Thompson and Scott, 1970) and alopecia, vascular changes, cataract, poor growth, and reproductive failure in rats (Wu, et al. 1979).

The metabolic basis for the nutritional relationship between selenium and the fat soluble antioxidant vitamin E was clarified when it was discovered that the peroxide-destroying enzyme, glutathione peroxidase, contained selenium (Rotruck, et al. 1973). Both nutrients, selenium as well as vitamin E, are part of cellular defense mechanisms against peroxidative damage (Hoekstra, 1975).

Because of the established role of selenium in animal nutrition, attention has recently been directed toward its possible role in human nutrition. Several lines of evidence suggest that selenium may indeed be a required nutrient for humans. Glutathione peroxidase isolated from human erythrocytes contains selenium (Awasthi, et al. 1975) and selenium stimulates the growth of human fibroblasts grown in cell culture (McKeehan, et al. 1976). Children with kwashiorkor have low blood selenium levels (Burk, et al. 1967) and administration of selenium to such children has been reported to result in enhanced growth and a reticulocyte response (Hopkins and Majaj, 1967).

Perhaps the first clinical case of human selenium deficiency was a long term total parenteral nutrition (TPN) patient from New Zealand, a low selenium area (Van Rij, et al. 1979). The patient developed bilateral muscular discomfort in the quadriceps and hamstring muscles 30 days after TPN was initiated. Addition of 100 μg of selenium as selenomethionine daily to the TPN solution eliminated all muscle symptoms within a week and full mobility was restored.

Additional evidence in support of a beneficial role for selenium in human nutrition comes from the People's Republic of China where an endemic cardiomyopathy known as Keshan disease has been associated with a low selenium status (Keshan Disease Research Group, 1979a,b). Keshan disease is limited to those areas of China in which the residents have low hair and blood selenium levels, low whole blood glutathione peroxidase activities, and dietary selenium intakes of less than 30 µg/day. This condition is characterized by gallop rhythm, heart failure, cardiogenic shock, abnormal electrocardiograms, and heart enlargement. The target population is primarily children from one to nine years of age, although women of child-bearing age are affected also.

An intervention trial with sodium selenite carried out with children one to nine years old who lived in an area affected by Keshan disease was highly effective in preventing the disease (Table 10). Doses of sodium selenite of 0.5 mg weekly for one to five year olds and 1.0 mg weekly for six to nine year olds essentially eliminated the disease in a previously afflicted geographic area. Except for some isolated cases of nausea, the sodium selenite caused no side effects in these trials. Physical examinations and liver function tests revealed no hepatic damage in children who had ingested the selenium tablets for three to four years.

The importance of selenium in human nutrition has received official recognition in that the Food and Drug Board of the National Research Council has recently established a safe and adequate range of intakes for selenium in adults of 50 to 200 µg/day (NAS, Food and Nutrition Board, 1980), with correspondingly lower ranges for infants and children (Table 11). Any daily intake within the recommended ranges is considered adequate and safe, but the recommendations do not imply that intakes at the upper limit of the range are more desirable or beneficial than those at the lower limit.

TABLE 10

Effect of Selenium on Keshan Disease in Children*

Treatment	Year	Number of Subjects	Number of Cases	Outcome of Cases				
				Alive	Turned Latent	Improved	Turned Chronic	Death
Placebo	1974	3,985	54	27	16	9	2	27
	1975	5,445	52	26	13	10	3	26
	1976	212	1	1	0	0	1	0
Sodium selenite	1974	4,510	10	10	9	0	1	0
	1975	6,767	7	6	6	0	0	1
	1976	12,579	4	2	2	0	0	2
	1977	12,749	0	0	0	0	0	0

*Source: Keshan Disease Research Group, 1979a

TABLE 11

Safe and Adequate Ranges of Daily Selenium Intake*

Group	Age (years)	Daily Selenium Intake (μg)
Infants	0-0.5	10-40
	0.5-1	20-60
Children	1-3	20-80
	4-6	30-120
	7+	50-200
Adults		50-200

*Source: NAS, Food and Nutrition Board, 1980

CRITERION FORMULATION

Existing Guidelines and Standards

In 1942, the U.S. Public Health Service (U.S. PHS, 1962; McDermitt, 1973) established 50 μg/l as the maximum level of selenium permissible in the finished water of Interstate Carrier water supply systems. When the standards were re-evaluated and revised in 1962, the maximum permissible level was reduced to 10 μg/l [U.S. Public Health Service (U.S. PHS), 1962]. The U.S. EPA (40 FR 248 59566) has established the 0.01 mg/l limit as part of the U.S. Environmental Protection Agency National Interim Primary Drinking Water Regulations that went into effect in June of 1977. According to the Safe Drinking Water Act (U.S. EPA, 1974) this level now applies to all utilities that serve 25 persons and/or have 15 service connections.

As previously summarized for children of school age (Table 11), the recommended daily allowance (RDA) of selenium is estimated to range from 0.01 to more than 0.10 mg/day. Individuals beyond school age require 0.05 to 0.2 mg/day (NAS, Food and Nutrition Board, 1980).

The threshold limit value (TLV) set for the time-weighted average concentrations of selenium in air for a normal 8-hour workday or 40-hour workweek is 0.2 mg/m^3 [American Conference of Governmental Industrial Hygienists (ACGIH), 1977].

The Food and Drug Administration (38 FR 81 8229) has ruled that sodium selenite or sodium selenate may be added to the complete feed for swine and chickens up to 16 weeks of age at a level not to exceed 0.1 μg/g, and for turkeys not to exceed 0.2 μg/g.

Current Levels of Exposure

It is estimated that the average adult intake of selenium is roughly 130 to 150 μg of selenium each day from food (Watkinson, 1974; Schroeder, et al. 1970). However, it is well known that the level of selenium in food is very dependent on the amounts in the soil and water where the food is grown or in the feeds that the livestock eat (Levander, 1976). The range of levels for specific vegetables grown in nonseleniferous versus seleniferous areas are: potato (0.005 to 0.940 μg/g), tomato (0.005 to 1.22 μg/g), carrot (0.022 to 1.30 μg/g), cabbage (0.022 to 4.52 μg/g), and onion (0.015 to 17.8 μg/g). Hence, persons living in areas where the selenium content of the soils is high will likely be exposed to daily dietary levels above 150 μg.

Levels of air selenium in municipalities and communities range from 0.0025 $\mu g/m^3$ to 0.0097 $\mu g/m^3$ (Dams, et al. 1970; Harrison, et al. 1971; Pillay, et al. 1971). Assuming average total daily inhaled volumes of 21.2, 11.1, and 1.4 cubic meters for men, women, and infants (0 to 11 weeks old), the estimated ranges of daily selenium exposures from ambient air are 0.053 to 0.206 μg, 0.028 to 0.108 μg, and 0.004 to 0.014 μg, respectively; estimated volumes of inhaled air are based on time-weighted averages of Tidal Volumes and Respiratory Frequencies (CIBA GEIGY, Ltd., 1970). Clearly, selenium in ambient air does not contribute significantly to the overall selenium exposure level of the general population. Levels of exposure from use of selenium based shampoos are unknown.

Special Groups at Risk

Individuals living in areas where selenium is found naturally at high concentrations (i.e., the Great Plains region and the southwestern United States) experience higher levels of exposure through food and drinking water than do the rest of the population and may therefore be more at risk due to excessive selenium intake (see Tables 2 and 3).

Very young children residing in high selenium regions might be especially at risk in that their liquid to body weight intake ratio is higher than that for adults, and thus their exposure to higher selenium concentrations may be excessive.

Individuals with diets deficient in vitamin E may also be especially at risk since growth inhibition results from synergistic effects of high selenium levels and vitamin E deficiency.

Basis and Derivation of Criterion

The question of the carcinogenic potential for ingested selenium has been reviewed in recent years by the National Academy of Sciences while studies by the National Cancer Institute (NCI, 1978) have added new but inconclusive evidence to the issue. NAS (1977) states that although the 1962 drinking water standard was recommended at 10 µg/l because of evidence that selenium was carcinogenic in animal studies, "a current literature review of animal studies does not support this contention."

An NCI bioassay of selenium disulfide at 100 mg per kilogram has been reported to cause the induction of hepatocellular carcinomas in female mice. This is consistent with an earlier report by Nelson, et al. (1943) that seleniferous grains and ammonium potassium selenide at 10 ppm induced liver tumors in rats. However, several inconclusive and negative carcinogenesis studies of selenite and selenate compounds ranging from 2 to 15 ppm have been reported since Nelson's work.

Despite many studies on experimental animals exposed to selenite or selenate salts, as well as epidemiological studies of man, no conclusive evidence has emerged that salts of selenium are carcinogenic. The carcinogenicity of selenium compounds is a complex issue because: (1) there is evidence that selenates, selenites, and selenides at non-toxic levels inhibit the development of spontaneous tumors, protect against the induction of tumors by known carcinogens, counteract the promotion of tumors in mouse skin initiator-promoter experiments, and inhibit the mutagenic action of chemicals in bacteria; (2) human cancer mortality at several organ sites appears to be negatively correlated with estimated selenium dietary intake and blood selenium levels, according to a tabulation of data from several countries; (3) even at moderate concentrations (5 to 10 ppm) of selenates and selenites the chronic toxicity is high, and this toxicity interferes with the development of tumors because of early deaths; (4) the aqueous solubility, and, therefore, the availability of different selenium compounds for absorption from the GI tract is markedly variable; (5) low concentrations of selenium (0.01 to 0.2 ppm in the diet) appear to be nutritionally essential; and (6) the reports of the chronic toxicity studies are difficult to compare because of the large number of different selenium compounds studied, the dependence of tumor induction on changes in protein and selenium levels in the diet, and the incomplete histopathological examination performed in many of the available studies. For these reasons it does not seem reasonable to use carcinogenic toxicity and risk as a basis for health criteria without additional research.

Obviously, one of the major factors involved in estimation of the minimum dose of selenium required to produce chronic toxicity in man or animals is the criterion, or definition, of chronic toxicity. The National Academy of Sciences (1976) has reviewed the literature in an attempt to establish a "no effect" dose level for selenium and thus to arrive at some conclusion concerning the level in water that can be expected to injure man. From this review, they found that the growth rate for rats fed a normal diet was inhibited if exposed to 4 to 5 µg/g of selenium in the diet. Only 1 µg/g of selenium in the diet was required to reduce growth in rats fed a diet severely deficient in vitamin E. Hadjimarkos (1971) has demonstrated in rats that selenium added to drinking water at a level as low as 2.3 mg/l during tooth development increases the incidence of caries. The National Academy of Sciences (1976) suggests that if histopathologic observations are used as the criterion for chronic toxicity, then 1 µg/g of selenium in the diet or 1 mg/l of selenium in drinking water may be shown to be sufficient to produce toxicity. However, it is recognized that the physiologic significance of the findings may not be clear, and the same may be said for biochemical parameters indicating that even lower levels can be toxic.

The amount of selenium needed to prevent deficiency diseases in animals is very small; 0.1 µg/g in the diet is a nutritionally adequate level for most species. Such a level translates into a human requirement of about 60 to 120 micrograms per day depending on the biologic availability in the diet, a person's physiologic status with regard to nutrients, and other factors (Jour. Am. Dietetic Assoc., 1977; Levander, 1976). This range compares well with NAS Food and Nutrition Board (1980) recommended human daily requirement range of 10 to 200 µg/day for selenium. Further, it is estimated that on the average, adults intake roughly 130 to 150 µg of selenium per day from food (Watkinson, 1974; Schroeder, et al. 1970). Levander (1976) has estimated that an average 6-month-old infant consumes 28 µg of selenium per day from food.

The uneven distribution of selenium in the soils of the United States could conceivably cause persons living in low-selenium areas and consuming only locally produced foods to develop a selenium deficiency, just as some who live in high-selenium areas may ingest excess selenium. However, most nutritional authorities agree that there is currently no evidence of selenium deficiency in human populations in the United States, probably because of the interregional food shipment that characterizes our present-day food supply (Jour. Am. Dietetic Assoc., 1977; Levander, 1976). Hence, there is no need to use water as a vehicle for supplementing the diets of the general population.

In consideration of the probable importance selenium plays in the human diet, and the varied but definite exposure potential from food intake, drinking water, and other sources, the strategy for identifying a criterion level for ambient waters must be based on minimizing the likelihood of contributing a sufficient amount of selenium that would increase an average total exposure above a selected toxic level.

The growth inhibition with vitamin E deficiency would be the candidate of first choice for toxicity effect and extrapolation into human effects. However, the vitamin E circumstance would be a special situation for the average population. The Westermarck, et al. (1977) study proposed a safe human dosage of 50 µg Se/kg/day (3.5 mg/day intake assuming a human body weight of 70 kg). This was also considered to be a special situation not reflective of the average population since tumor patients were the sample subjects (e.g., their Se needs may be greater than the normal population as associated with positive cancer control aspects of Se nutrition).

Table 12 summarizes available no- and low-response levels discussed in this report. These animal data were considered along with human nutrition study information to develop a candidate toxicity level (i.e., for Se overdose response level not the Se deficiency end point). In this table the animal dietary concentrations were estimated and expressed as Se with no further consideration of differential compound bioavailability. Background Se diet concentrations were also not considered. From consideration of

TABLE 12

Summary of Low Level Response Effects (All Oral)

Compound Used in Test	Reported Oral Concentration and/or Dosage	Estimated[b] ppm Diet Se Concentration	Effects Response Rating	Species and Study Period	References
Sodium Selenite	4 ppm in water	<2[c]	dental caries --	rat	Navia, et al. 1968
Sodium Selenide	$\frac{5\text{-}12.5\ \text{mg}}{20\ \text{days}}$	≈4[d]	changes in endocrine glands	guinea pig 2 studies, 20 days	Vesce, 1974
Selenite or Selenate	0.5 µg/g diet[a]	≈0.3	decreased body weight	rat --	Tinsley, et al. 1967
Selenium "Compounds"	0.5 µg/g diet	≈0.3	chronic liver and bile hyperplasia	rat --	Harr and Muth, 1972
Selenium "Compounds"	0.25-0.75 µg/g diet	≈0.5	minimum toxic effects to organs	rat --	Harr and Muth, 1972
Selenite	2 µg/g diet	<1	no detrimental effects	hen 105 weeks	Thapar, et al 1969, with support from Poley, et al. 1941

TABLE 12 (cont.)

Compound Used in Test	Reported Oral Concentration and/or Dosage	Estimated[b] ppm Diet Se Concentration	Effects Response Rating	Species and Study Period	References
Selenium "Compounds"	1 µg/g diet	<1	toxic in vitamin E-deficient diet	rat —	National Research Council, 1976
Selenium	0.5 µg/g diet	0.5	"do not fare less well than lower diet controls"	cattle —	National Research Council, 1976

[a] the author assumes 200 g rats eating 10 g of food per day

[b] ppm (or µg/g) in diet expressed as Se (with no consideration of possible background food Se concentration)

[c] assumes daily water intake approximately same as diet (30 g food, 25 ml H_2O)

[d] assumes guinea pigs eat = 50 grams/day

estimated dietary Se intake concentration (see Table 12), a 0.5 ppm Se intake concentration was judged as representative of a lowest-observed-effect level (LOEL) for small animals (or specifically rats).

Assuming rats weigh 0.3 kg and their total diet is about 20 percent of their body weight as food and water (i.e, about 10 percent body weight as wet weight food and about 25 ml water) low response effects are demonstrated in rats at selenium levels of 0.1 mg Se/day (or 100 μg Se/day), as shown below:

$$\begin{array}{c}\text{0.5 ppm}\\ \text{selenium in diet}\end{array} = 0.5\ \text{mg/kg}$$

$$\text{intake} = 0.5\ \frac{\text{mg}}{\text{kg}}\ (0.2)\ 0.3\ \text{kg} = \frac{30\ \mu\text{g Se}}{\text{day}}$$

$$\text{animal dose} = \frac{30\ \mu\text{g/day}}{0.3\ \text{kg}} = \frac{100\ \mu\text{g Se}}{\text{kg body wt. per day}}$$

Converting this dose directly to humans (assuming 70 kg as an average human body weight) results in an equivalent human dose of 7 mg Se/day/human without consideration of safety factors, as shown below:

$$\begin{array}{c}\text{direct equivalent}\\ \text{human dose}\end{array} = (0.1\ \text{mg Se/kg/day})\ \frac{70\ \text{kg}}{\text{human}} = 7\ \text{mg Se/day/human}$$

Since Se is a nutrient and both human food exposure levels and human recommended daily allowances have been developed, a safety factor of 10 is recommended. An acceptable daily intake (ADI) of Se from food for humans is then proposed as 0.7 mg for protection against low toxic response effects.

It does not seem reasonable to permit the Se level in water to be more than about 5 to 10 percent of the dietary level since (1) populations living in seleniferous areas can be exposed to much higher levels of Se in both food and water and, (2) it is desirable to assure further protection of children from water concentrations which could result in combined dietary consumption (food and water) in excess of the low effect response levels.

A maximum water-related contribution of 35 μg Se/day is selected as protective (assumes 5 percent of the total dietary intake would be from water). Assuming that the average individual consumes 2 liters (2 kg) of drinking water per day and considering the marginal increase of dietary Se associated with eating 6.5 grams of fish with a bioconcentration factor of 6, the estimated concentration for water is calculated as follows:

$$\text{Criterion level} = \frac{35\ \mu\text{g Se/day}}{2 + (0.0065)6} = 16.6\ \mu\text{g Se/l}$$

Based on these calculations it appears that the U.S. Environmental Protection Agency Drinking Water Standard of 10 μg/l is probably an appropriate ambient criterion level to protect the health of the U.S. population.

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